"I would have everie man write what he knowes and no more."—MONTAIGNE

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EDITORIAL

SUCH is our ignorance of the innumerable processes and vital mechanisms which keep the internal environment constant, that it is not surprising that opinions differ as to how this dynamic balance, between the disturbing and restorative activities which we know as health, is kept. There are few subjects in medicine in which this difference of opinion is more marked than in that of spinal anaesthesia. On the one hand there are those who regard the giving of a spinal anaesthetic as little short of a criminal assault, and on the other those who look upon it as the best anaesthetic for all operations which require muscular relaxation below the diaphragm. Most of us would regard these positions as extreme. He who has little or no first-hand experience but has seen the tragedy of a meningitis or a paraplegia following puncture of the lumbar theca naturally inclines to the former view. There are others who count their successful applications of spinal anaesthesia by the thousand and who are disposed to think that there is a useful field for this type of anaesthesia.

Unfortunately the detached scientific assessment of the place that spinal anaesthesia should occupy in the measures at our disposal for facilitating the surgeon's task and at the same time preventing pain has apparently been rendered impossible.

It is well known that pent-up emotion must find an outlet and if we can blame the Germans or the Russians or the fellow next door for the terrible state of the world, it gives a great sense of relief. It is also so much easier to blame somebody than find out what is wrong—a difficult, tedious and doubtful process that doesn't help us to hate anybody and may even discover some elements of unreason in ourselves. Such effort is exhausting and the satisfaction gained modified thereby.

The entrance of the emotions into matters which ought to be settled by reason and experience has had some strange results. A witness at a recent trial gave it as his opinion that it was the anaesthetic itself that had caused the mischief. How would he have explained the fact that in thousands, even in tens of thousands, of other cases this same anaesthetic had failed to do any damage? At a meeting of anaesthetists a man of some experience told us that he had given up using spinal anaesthesia and substituted for it a variety of the "cocktail" type. In the course of this conversion he had found that it was unwise to exceed a dose of morphia greater than from 1/24 to 1/12 grain (2.5–5 mg) but he used pethidine 50 mg. repeated when required! Apart from these extreme examples of gentlemen who have apparently lost the use of their judgment, we are suggesting that there are many who have allowed it to be swayed by their fear of litigation. It is natural for every anaesthetist to consider his methods the best, otherwise he would presumably change them; but although they may be the best for him it by no means follows that they are the best for the patient. "The anaesthetic of choice" is a phrase that has been applied to most of the methods in use. It affords a curious example where the introduction of the personal possessive pronoun "my" would have been both more modest and more accurate. Chloroform is out, spinal anaesthesia, so it would appear, is on its way out, ether has been threatened, nitrous oxide has been known to be followed by not only death but insanity, and the latest reports from America suggest that the deaths following curare are six times as numerous as when the drug is omitted. It seems possible that some anaesthetist in the near future, in his enthusiasm for a plaintiff's case and his own

" method of choice " may describe any of the foregoing well-established methods as little short of criminal assault!

This emotional element has recently entered the domain of spinal anaesthesia, and the circumstance of its birth is certainly the tendency of the public to resort to litigation to redress the ills, real or imaginary, inflicted on them by operations undertaken in all good faith for their benefit. Every operation, every anaesthetic, even every injection carries with it some risk, a risk in addition to the one due to man's natural tendency to err. When damage follows the injection of an anaesthetic into the lumbar theca, the relationship between cause and effect *seems* to be closer than with some other procedures and the victim of such damage feels he has a more obvious claim to compensation. Every surgeon and every anaesthetist of experience knows that it is the apparent obviousness of the connection and not necessarily the fact of it that makes this form of anaesthesia specially liable to litigation. " That in fact the dangers of neurological damage following properly administered spinal anaesthesia are not out of proportion to the dangers attendant upon properly administered clinical anaesthesia ", is suggested by the report of Dripps and Vandam (1954) who have recorded 10,098 spinal anaesthetics without any major neurological sequelae being detected in the long term follow-up. These authors conclude with the words, " some have taken the view that spinal anaesthesia will soon be of 'historical interest only', the results of this long-term study did not suggest such a position, they even suggest the possibility that such an attitude might deprive patients of a safe method of anaesthesia ".

It is surely time to see where we are tending. Differences of opinion must not be exaggerated into wholesale condemnation of the other fellow's " method of choice ".

New ideas resulting in new techniques are to be welcomed in the cause of progress. All take their toll of victims, it takes time for the accurate appraisal of their advantages and disadvantages, to tell in fact whether the progress is forward or backward. Dr. Ralph Waters (1948), himself the introducer of cyclopropane, the closed circuit and other " innovations ", has warned us that it is unwise to embrace the new because it is new, and equally so to discard the old because it is old.

OUR next issue will be an Educational Number, the subject matter of which should be of considerable use to postgraduates of the specialty studying for examinations. This will take the place of the Educational Supplement which was a feature of the Journal last year, and it is intended that two such Educational Numbers will appear annually.

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SOME CIRCULATORY ASPECTS OF INDUCED HYPOTENSION WITH HEXAMETHONIUM

BY

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INTRODUCTION

AFTER preliminary experience with the use of induced hypotension with hexamethonium under general anaesthesia in the United Sheffield Hospitals, it was thought useful to investigate, as far as possible, certain functions of the cardiovascular system under induced hypotension, in an attempt to test the validity of certain assumptions and hypotheses previously made when the technique was introduced. The clinical observations are based on a series of 1,029 documented cases performed in the United Sheffield Hospitals, and reported elsewhere (Griffiths, 1953a); 406 of these patients were personal cases.

The investigations fall naturally into the following sections to be discussed separately:

(i) The bleeding time under induced hypotension, and the problem of reactionary haemorrhage.

(ii) The circulation time, and the effect of posture.

(iii) The accuracy of methods used for the measurement of the blood pressure at the low levels of induced hypotension.

(iv) The recovery of the blood pressure in the postoperative period.

(v) The remaining pressor responses under induced hypotension.

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THE BLEEDING TIME AND REACTIONARY HAEMORRHAGE

The bleeding time was estimated in 100 patients, in an attempt to test Enderby and Pelmore's (1951) hypothesis regarding the mechanisms for the arrest of haemorrhage under hypotension. The method used, a "Modified Ivy" (Ivy, Shapiro and Milnick, 1935), was as follows: a sphygmomanometer cuff was applied to the arm, inflated to 40 mm Hg and held at this pressure. For this purpose, the control devised by Williams (1951) proved useful. The forearm was cleaned with 70 per cent spirit, and the spring-gun, set at 3 mm depth making three vertical incisions approximately two inches apart, was used, taking care to avoid surface veins. The stop-watch was started immediately the first stab was made; at 15-second intervals thereafter, blood was carefully removed from each wound on separate pieces of prepared and numbered filter-paper. This latter was applied carefully to avoid removing any coagulum-formation. The end-point between bleeding and the final slight ooze must be distinguished. When all the wounds had ceased to bleed, the average of the readings, to the nearest 0.1 minute, was taken as the bleeding time; the normal time by this method is less than five minutes.

All the 100 patients were males, between the ages of 18 and 50 years, with

no complicating clinical disease, and all had a normal bleeding time pre-operatively. They all received premedication with papaveretum and scopolamine, induction with thiopentone sodium, followed by maintenance with endotracheal nitrous oxide-oxygen (4 l.: 2 l., or 4 l.: 1½ l./min) on the semi-closed circuit with circle carbon dioxide absorption, after the larynx and trachea had been thoroughly sprayed with 4 per cent lignocaine; maintenance was supplemented by intravenous pethidine in 1 per cent solution. Fifty cases were anaesthetized by this technique; the remaining fifty received induced hypotension with hexamethonium in addition. The results are shown in table I. The "Pre" column refers to bleeding times estimated before any medication had been given, and the "Post" column contains the values obtained 30 minutes after induction of anaesthesia. In all the hypotensive cases, the systolic blood pressure was between 65 and 80 mm Hg, this state being present for at least 10 minutes before the "Post" value was obtained. The results have been compared statistically (table II); the conclusions drawn are that, in both groups of patients, there was a significant but small increase in the bleeding time during this form of anaesthesia, but that there was no significant difference between the increases in the two groups. Induced hypotension with hexamethonium thus appears to have no effect on the bleeding time in the normal male patient.

The technique of hypotension with vasodilatation might, at first sight, be expected to lead to many cases of reactionary haemorrhage on the return of the blood pressure to normal, but the

TABLE I

Bleeding times (to nearest 0.1) in minutes in 100 cases

All were males, aged 18–50 years, with normal bleeding times. All received the same premedication and anaesthesia: Group II received in addition, induced hypotension with hexamethonium, with a systolic blood pressure of between 65 and 80 mm Hg.

"Pre" columns: values before premedication.

"Post" columns: values 30 minutes after the induction of anaesthesia.

GROUP I				GROUP II			
Pre	Post	Pre	Post	Pre	Post	Pre	Post
3.7	4.1	2.8	3.2	4.1	4.4	3.9	4.2
2.9	3.6	5.0	4.9	3.6	4.0	4.1	4.4
4.6	4.8	4.1	4.3	3.2	3.3	3.3	3.6
3.2	3.5	3.9	4.3	4.7	4.8	3.7	3.9
4.1	4.2	4.1	4.4	3.8	3.9	4.0	4.4
3.8	4.0	3.8	4.1	4.1	4.5	2.9	3.5
3.5	3.9	3.5	3.8	2.6	2.8	3.2	3.4
4.2	4.1	4.0	4.2	4.6	4.2	3.8	3.7
3.3	3.6	3.7	3.8	3.9	4.3	3.9	4.1
4.4	4.9	3.6	3.6	4.7	4.9	4.7	5.1
3.6	3.9	4.1	4.3	5.0	5.2	4.6	4.7
3.8	4.1	5.0	5.3	3.6	3.9	3.9	4.1
4.9	5.1	3.6	3.8	4.2	4.5	3.8	4.2
3.6	3.7	3.1	3.2	3.8	4.2	4.3	4.8
4.7	5.1	4.1	4.3	3.9	4.1	3.5	3.6
3.8	3.8	3.9	4.1	4.4	4.8	3.1	3.0
2.2	2.4	3.7	3.7	3.7	3.9	3.8	3.9
4.0	4.2	4.2	5.0	4.1	4.5	4.1	4.4
3.6	3.6	4.8	5.1	3.5	3.9	5.0	5.2
4.1	4.3	3.1	3.3	2.9	3.1	3.8	4.1
3.5	3.8	2.6	2.9	4.1	4.1	3.3	3.5
3.9	3.7	4.4	4.6	2.8	3.1	3.7	3.9
4.5	4.7	4.8	5.2	3.7	3.9	4.6	4.8
3.6	3.9	3.9	4.1	3.6	4.0	3.9	4.1
4.0	4.5	3.4	3.9	4.2	4.3	3.8	3.9

TABLE II

Statistical Analysis of the Results in Table I

The "t"-test was applied to the difference between the "pre" and "post" induction values for each patient.

	Mean difference	S.E. of difference	"t"	P
Group I	+0.236	±0.0277	8.52	0.1%
Group II	+0.232	±0.0238	9.75	0.1%

Thus in both groups there is a significant increase in the bleeding times in the post-induction values. The "t"-test also shows that there is no significant difference between the increases in the two groups.

mechanism for the arrest of bleeding in these circumstances has been outlined by Enderby and Pelmore (1951). They maintain that, although the vessels are dilated, clot forms normally at the end of the cut vessel, and because of the low head of arterial pressure, intimal retraction is sufficient to retain the clot in position. During the gradual recovery phase of the blood pressure, vasoconstriction progressively increases, and the vessel wall becomes more and more closely applied to the thrombus. These workers suggest that these conditions are preferable to the effects of vasoconstrictive drugs injected locally for the reduction of haemorrhage, since, when such constriction passes off, postoperative bleeding and oozing are more likely. The findings in this investigation of bleeding time confirm the first part of Enderby and Pelmore's theory.

It is essential, however, as McLaughlin and Watson (1951) point out, that the surgeon must have a full appreciation of this mechanism, and must also understand fully the necessity for securing any vessel of size seen, either by ligation or diathermy, whether that vessel is bleeding or not. The only danger in the United Sheffield Hospital series has come from unsecured large vessels, especially veins, or from arteries inside cavities.

In this series, the results, from the point of view of the effect on the reduction of bleeding during operation, were classed as:

(i) *Excellent*: this implied a perfectly clear operative field, with only a very slight capillary ooze, and a very small blood loss.

(ii) *Very satisfactory*: into this class fell those cases with a clear operative field, with no troublesome bleeding, but where the total blood loss was appreciable—that is, over 100 ml.

(iii) *Failure*: This group contained all the cases not falling into the previous two categories.

There were five cases of reactionary haemorrhage out of the total of 1,029 patients:

(1) *First-stage thoracoplasty*: Male, aged 28. "Excellent" result. Twenty hours postoperatively it became obvious that a large blood loss had occurred; whole-blood transfusion was performed (total 1,500 ml), and his condition improved. The second stage operation was carried out sixteen days later under general anaesthesia without hypotension. A very large quantity of blood clot was evacuated from the extrapleural space, and it was seen that the anterior communicating branch of the internal mammary artery in the third intercostal space was bleeding, now that the pressure of the clot had been removed. No attempt had been made at the first operation to secure any of these vessels. The further course was uneventful.

(2) *Extensive skin-flap*: Male, aged 38. Operation was begun before full hypotension was induced, and bleeding occurred from the first part of the incision; some twelve minutes elapsed before "very satisfactory" conditions were established. Postoperatively a haematoma formed in this initial area but not in the rest of the flap.

(3) *Radical mastectomy*: Female, aged 42. "Very satisfactory" result. Many of the branches of the axillary vessels were neither ligated nor diathermized. There was a very large postoperative blood loss and the patient required a large transfusion of whole blood (1,800 ml). On exploration under general anaesthesia, there was a large branch of the axillary vein bleeding steadily: it was ligated. Good recovery.

(4) and (5) Both extensive skin-flaps: slight oozing for ten to twelve hours postoperatively, prejudicing neither the patients nor the surgical results.

THE CIRCULATION TIME

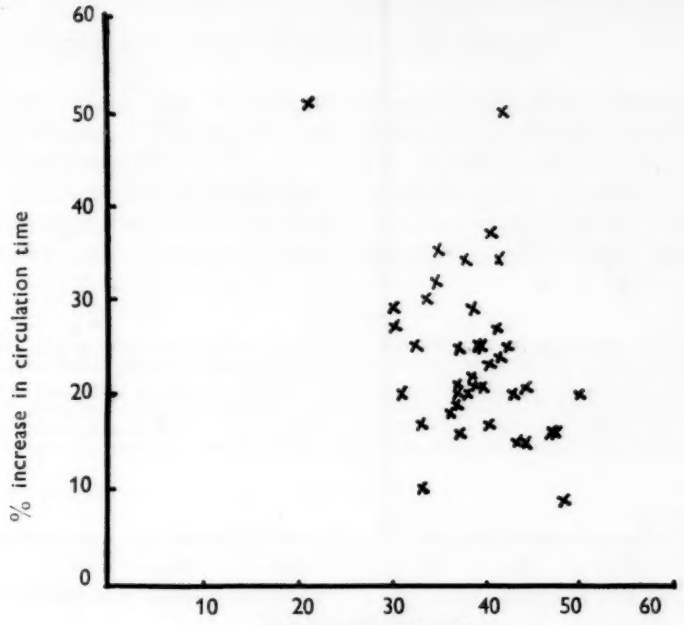
In considering methods of measuring the circulation time in the patient under general anaesthesia, with or without induced hypotension, it is clear that the employment of an "objective end-point" is obligatory. Furthermore, the method must be safe, simple, efficient and speedy, interfering neither with the anaesthesia nor the theatre team, and without the need for complicated apparatus. It must be capable

of being repeated at short time intervals. One of the most attractive methods is that described by Macgregor and Wayne (1951), employing intravenous fluorescein and histamine skin weals: this method can be used to determine, for example, the "foot-minus-arm" time, thus eliminating the variables of the pulmonary circulation, and measuring the speed of the circulation in arterial segments of various parts of the body. Although this method has been used successfully during plastic surgery (Hynes and Macgregor, 1949), its use was regretfully deemed inadvisable in this work, since a darkened theatre, standard conditions of skin temperature and a source of ultraviolet light are required. After preliminary trials the "arm-respiratory centre" (sometimes known as the "arm-carotid sinus") determination using intravenous theophylline - ethylenediamine, as described by Koster and Sarnoff (1943) and Ross (1951) was found to satisfy the criteria already described. The method was derived from the use of the drug in preventing postoperative pulmonary collapse (Sperling, Weisman and Papermaster, 1942). The end-point with this method is an inspiratory gasp in 90 per cent of cases, but may be a swallow or expiratory catch in the remaining 10 per cent; in the conscious patient, no difficulty was found in defining the end-point exactly, but preliminary tests showed that only under the very lightest anaesthesia was the end-point so clear by direct observation. This difficulty was overcome by attaching the patient to a recording spirometer, which in nearly all cases demonstrated the end-point conclusively.

The method is as follows: theophylline-ethylenediamine, as "Cardophylline", was used in ampoules of 480 mg in 2 ml. One ml of this solution in a 10-ml syringe with a blunt-bevelled (F.G. 20) needle was used for each determination. The veins employed were the median cubital in the anticubital fossa, or the internal saphenous at the medial malleolus. Venous stasis resulting from limb constriction was allowed to subside before the dose of the drug was rapidly injected. At the same time, the stop-watch was started (after a little practice this manoeuvre presented no difficulty to the single-handed operator); the end-point was observed and the time-interval noted. Ross (1951) employed this method in both normal and diseased patients and he observed no complications apart from local reactions where a perivenous leak had occurred; severe pain resulted but neither thrombosis nor necrosis. Scrupulous attention was paid to eliminating this complication in the present investigation. In three cases, the end-point in one or more determinations was not completely definite, and these cases were excluded from the results.

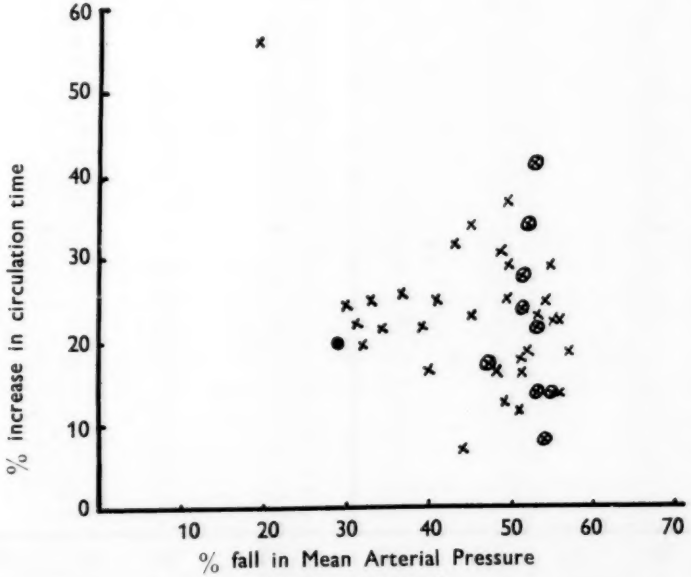
In all 40 patients, the arm-respiratory centre time was measured before the premedication. This time was redetermined after the induction of smooth anaesthesia with thiopentone, nitrous oxide-oxygen, pethidine.

The arm-centre time was again found after the induction of hypotension with hexamethonium with a 5° foot down tilt, and again after a 15° foot down tilt. In the first and third ten cases, the ankle-respiratory centre time was measured after the induction of anaesthesia, and again in the two foot down positions after the induction of hypotension. The ankle-centre time was again determined in ten



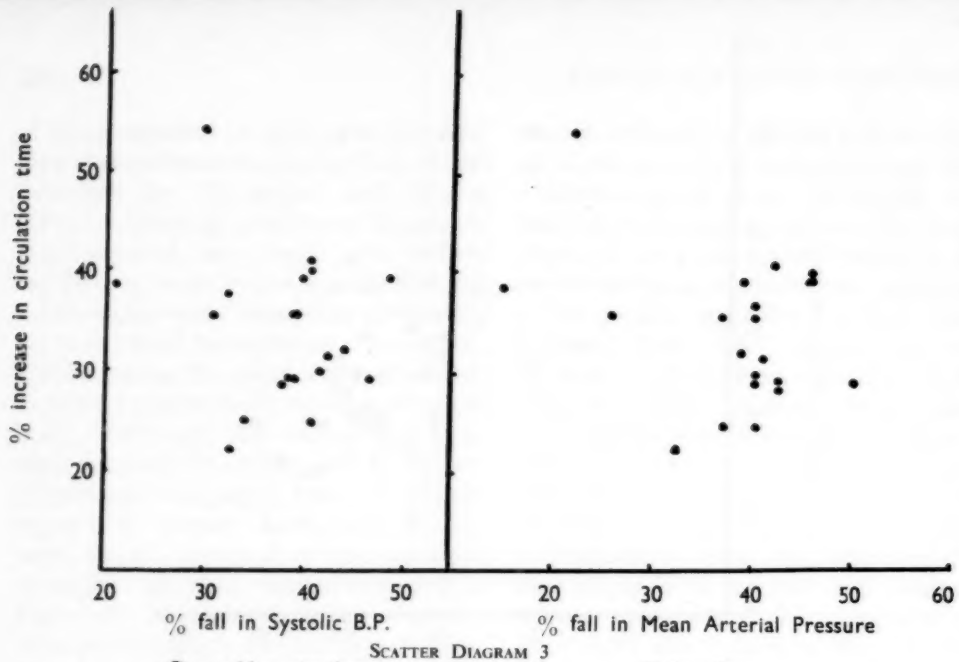
SCATTER DIAGRAM 1

× = arm-centre times. 5° foot down.



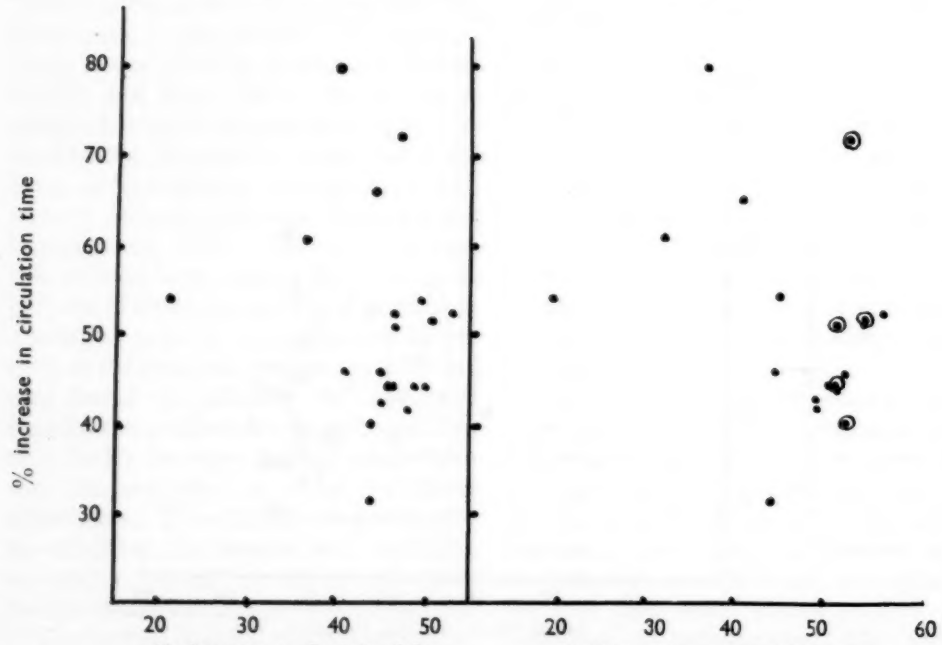
SCATTER DIAGRAM 2

Cross = arm-centre times.
Cross in circle = assumption of diastolic pressure of 30 mm Hg. 15° foot down.



SCATTER DIAGRAM 3

● = ankle-centre times. 5° foot down.



SCATTER DIAGRAM 4

● = ankle-centre times. ⊙ = presumed diastolic pressure of 30 mm Hg. 15° foot down.

alternate cases when the horizontal position was restored. The results are shown in tables III and IV.

Thus the values before premedication are comparable with those found by Ross (1951). This worker, in 150 normal cases, found a range of 6.8–22.0 seconds, with a mean of 12.1 seconds, standard deviation 2.3. In the present series, there was no alteration in the circulation time after the induction of anaesthesia. Both the arm-centre and ankle-centre times were in-

TABLE III

Arm-respiratory centre circulation times in seconds (to nearest 0.2) with theophylline-ethylenediamine, and blood pressures, before and after anaesthesia, and after induced hypotension with hexamethonium.

The pre-operative data agree with those of Ross (1951). Range 7.2–18.0, mean 11.9, S.D. 2.5. There was no alteration in circulation time after the induction of anaesthesia, but there was an increase after the induction of hypotension: this increase had no quantitative relation to the degree of blood pressure fall, and was not altered by an increase in the foot-down tilt (cf. ankle-centre times in table IV and scatter diagrams 1–4).

Pre-operative		Post-anaesthetic		Post-hypotension, 5° foot-down tilt		Post-hypotension, 15° foot-down tilt	
Sec	B.P.	Sec	B.P.	Sec	B.P.	Sec	B.P.
7.2	124/68	7.6	114/60	9.8	80/45	9.6	68/40
10.8	132/74	10.6	124/65	13.0	75/42	13.2	70/35
12.0	116/60	11.8	124/64	14.2	85/50	14.2	78/46
15.0	142/82	15.2	128/74	18.4	78/44	19.0	66/38
14.4	128/88	14.8	130/72	16.2	68/40	16.0	65/?
18.0	130/80	17.6	122/76	19.4	82/50	18.8	68/42
14.4	118/72	14.0	116/76	16.4	78/40	16.0	65/?
11.2	164/84	11.6	128/74	13.4	68/35	13.8	60/30
10.2	132/68	10.6	146/74	12.8	82/50	13.0	75/44
11.6	142/80	12.0	118/76	15.0	74/40	14.8	65/30
13.4	126/64	13.6	120/66	15.8	76/36	15.4	68/30
9.2	132/76	9.4	122/70	12.2	82/52	12.4	74/38
14.0	120/68	14.2	126/66	17.2	84/60	17.6	76/52
10.8	118/64	10.2	120/68	12.8	82/54	12.8	74/48
12.2	136/74	12.0	118/66	14.4	74/40	14.0	66/32
13.0	148/78	13.2	116/70	15.8	72/30	15.6	64/?
9.4	130/64	9.2	122/66	12.4	80/40	12.6	68/30
14.2	142/76	14.2	132/70	17.6	78/36	17.4	64/?
11.0	126/68	11.4	118/68	13.6	74/50	13.8	68/42
14.0	138/70	13.8	136/66	16.2	82/54	16.8	78/50
8.2	148/78	8.4	116/72	12.6	68/36	12.0	62/?
7.4	112/60	7.8	114/64	11.8	90/58	12.2	90/54
15.0	128/78	14.4	120/70	16.6	68/42	16.2	64/32
12.2	134/70	12.4	116/70	16.6	68/40	16.6	62/?
11.8	122/66	12.0	128/62	15.0	74/38	15.4	64/?
13.0	138/68	12.6	128/66	15.8	78/36	15.6	68/?
10.2	122/76	10.2	126/68	13.0	74/44	13.2	68/32
12.6	138/80	12.8	126/72	15.6	78/42	15.2	64/32
9.0	122/68	8.8	116/64	11.6	76/38	11.8	68/32
13.2	132/82	13.0	118/76	16.2	72/44	16.8	62/30
8.8	156/78	8.6	123/72	11.8	74/40	12.2	65/?
10.2	116/66	10.4	126/70	13.2	88/54	12.8	84/50
14.2	140/78	14.2	136/74	17.0	78/38	17.4	66/30
11.6	128/68	12.0	124/74	13.8	70/36	14.2	68/34
10.4	137/82	10.2	144/78	12.2	72/44	11.6	64/34
11.4	134/86	11.6	128/72	13.4	68/32	13.2	62/?
14.0	122/74	14.0	120/70	17.0	74/50	17.2	68/46
11.4	132/78	11.2	126/74	14.4	78/36	14.0	65/30
15.2	148/82	15.2	116/80	18.0	74/40	17.8	68/34
12.0	122/66	12.2	134/72	16.4	84/58	16.0	74/50

TABLE IV

Ankle-respiratory centre circulation times in seconds (to the nearest 0.2) and blood pressures, in the first and third ten patients of table III.

There was an increase in circulation time after hypotension (not related to the degree of blood pressure fall), and a further increase when the foot down tilt was increased. Resumption of the horizontal position tended to restore the circulation time.

Post-anaesthetic		Post-hypotension, 5° foot-down tilt		Post-hypotension, 15° foot-down tilt		Post-hypotension, horizontal	
Sec	B.P.	Sec	B.P.	Sec	B.P.	Sec	B.P.
11.8	114/60	17.6	80/45	21.2	68/40		
14.8	124/65	20.6	75/42	24.6	70/35	21.0	78/44
17.0	124/64	23.2	85/50	27.4	78/46		
19.2	128/74	26.2	78/44	27.2	66/38	25.6	75/48
19.0	130/72	26.4	68/40	28.8	65/?		
22.2	122/76	27.0	82/50	29.2	68/42	26.8	78/50
20.6	116/76	26.8	78/40	28.8	65/?		
15.2	128/74	19.6	68/35	23.2	60/30	20.0	70/40
15.0	146/74	20.0	82/50	23.2	75/44		
16.6	118/76	21.2	74/40	24.2	65/30	21.0	75/45
14.0	116/72	19.6	68/36	24.2	62/?		
13.6	114/64	18.8	90/58	21.0	90/54	19.2	98/60
19.4	120/70	25.6	68/42	28.0	64/32		
18.0	116/70	25.4	68/40	27.2	62/?	25.0	72/48
17.2	128/62	22.0	74/38	24.8	64/?		
18.2	128/66	23.4	78/36	26.2	68/?	24.0	80/40
16.8	126/68	21.0	74/44	24.0	68/32		
18.0	126/72	23.2	78/42	26.0	64/32	23.0	80/48
13.8	116/64	17.2	76/38	20.2	68/32		
19.0	118/76	25.8	72/44	28.8	62/30	26.2	82/50

creased after the induction of hypotension, although there was no quantitative correlation between this increase and the degree of hypotension produced. Increasing the amount of foot down tilt further prolonged the ankle-centre time, but did not affect the arm-centre time; restoration to the horizontal tended to restore the ankle-centre time. These findings agree with those of Guglielmi, Ramovecchi and Ricci (1952) in conscious patients (arm-tongue and leg-tongue times) and Van Bergen *et al.* (1954) in anaesthetized patients (arm-ear times). These latter workers, however, found in their one case that the alteration of the circulation time was an inverse function of the level of the systolic blood pressure.

These changes may be correlated with those described by Burt and Graham (1950), who showed that there was an increase in skin temperature and limb blood flow after hexamethonium, the increase in limb flow being greater, more regular and longer lasting in the legs than in the arms. Restall and Smirk (1952) have shown that after hexamethonium the body loses some of its capacity to resist the gravity pressure dilatation of its vessels (a similar loss occurs after nitroglycerine and is due to the direct paralysing action of this drug on the smooth muscle of the vessel walls), and these workers suggest that "gravitational hypotension" is a better term than "postural hypotension", since the phenomenon is present to some degree even in the horizontal position. This effect of diminished ability of the vessels to compensate for high intravascular pressures probably explains why there

is a greater fall in blood pressure in hypertensive patients than in normal individuals after hexamethonium, and why "postural hypotension" persists even when the "level" blood pressure is near normal. It is not feasible to attempt to explain the changes in circulation time by considering the physical laws concerning volume flow rate, lateral pressure and velocity of flow through a system of such widely varying cross-sectional and surface area as the peripheral vascular tree, especially as so many of the relative quantities are imprecisely known: moreover, the times measured in this work are mainly on the venous side of the circulation, which is obviously slowed. Further work, as by using the histamine weal method, would be necessary to make positive conclusions on the effects of induced hypotension on the velocity of the blood flow through the arterial section in whole or in part, of the peripheral vascular bed.

THE MEASUREMENT OF THE BLOOD PRESSURE

The blood pressure is usually measured clinically by means of a sphygmomanometer on the arm. To obtain consistently reliable and comparable figures, attention must be paid to seeing that the correct size of cuff is used (20 per cent wider than the diameter of the limb on which it is used, and sufficient to half-encircle it), that the bag is applied on the side of the brachial artery, and that the cuff is applied neatly, and is without bulges when inflated. The mercury manometer must be clean, its zero level correct, and the column vertical: the meniscus must be at eye level. In use the cuff is inflated rapidly, released slowly (Annotation, *Lancet*, 1951).

In some cases under hexamethonium induced hypotension the diastolic blood pressure becomes unrecordable by auscultation, and in order to investigate its level and to test the accuracy of the systolic pressure record as determined by auscultation with the mercury sphygmomanometer at low pressures, intra-arterial capacitance manometry was undertaken. The results in five cases are shown in table V, and the low pressure recording of the first case from this table is shown in figure 1. These results are interesting in that the level of the diastolic pressure by auscultation was taken at the point of disappearance of the auscultatory sounds, as well as at the point of "muffling". In these few cases, capacitance manometry indicates that the former point may be a more accurate measure of the diastolic pressure; this agrees with the recommendations of Bordley *et al.* (1951) and with the Joint Report of the Committees of the Cardiac Society of Great Britain and Ireland and the American Heart Association (1939). Indeed, when the pressure is low, there is frequently no "muffling" and disappearance of the sounds is the only criterion of the level of the diastolic pressure. Table V also shows that in three cases where

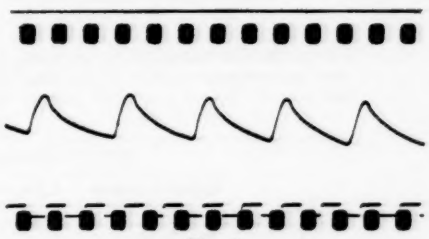


FIG. 1

Intra-arterial capacitance manometry recording of Case 1 of table V during the period of hypotension of 65/? mm Hg, showing the normal contour of the tracing at this low pressure.

the diastolic pressure was unrecordable by auscultation, there was a value by capacitance manometry of at least 30 mm Hg. The tracing in figure 1 shows that the contour of the pulse wave is of normal configuration at these low pressures.

Woodhall *et al.* (1954) recorded their comparisons of mean arterial pressures by intra-arterial capacitance manometry and arm-cuff records. They found that the sphygmomanometry readings were consistently higher than the direct records; whether the difference is mainly in the systolic or diastolic determinations, or in both, is not shown, as only mean pressures are described, the arm-cuff mean pressure being calculated as the diastolic pressure plus two-thirds of the pulse pressure. Moreover, these workers used an aneroid manometer, the use of which is not favoured in this country because of its notorious inaccuracy. For these reasons, it is difficult to compare their results with those in the present work.

It seems therefore that the careful use of auscultation mercury sphygmomanometry on the arm is a sufficiently reliable indication of the systolic blood pressure in the 60–80 mm Hg pressure range. Lower pressures than 60 mm Hg were considered inadvisable and therefore no comparisons below this figure are available, although it is of interest in this connection to note a phenomenon observed in two patients. Both patients were elderly, thin men, undergoing block dissections for malignant glands of neck. In consequence, the common and external carotid arteries were exposed throughout their courses in the neck. Both men had blood pressures of 80/50 mm Hg during the hypotension in the level position: normal arterial pulsations were seen and felt. A slight foot-down tilt (5°) reduced the pressures to 66/? and 68/? mm Hg respectively, but pulsation was still present and of good volume. A steeper tilt led to a rapid disappearance of a recordable systolic pressure and the abolition of visible pulsations in the carotid arteries, although palpation revealed a feeble pulse of a marked dicrotic character. Returning the patient to the horizontal restored the auscultatory blood pressure and the visible carotid pulsations, with a disappearance of the striking dicrotic pulse. These observations, and tracings from the cases in table V, as illustrated in figure 1, suggest that underfilling of the arterial system is not present under hexamethonium hypotension during anaesthesia until systolic pressures of below 65 are reached.

TABLE V

Comparison of values of the systemic blood pressure by mercury manometer auscultation sphygmomanometry on the arm and by intra-arterial (brachial artery) capacitance manometry, before and after induced hypotension with hexamethonium under general anaesthesia.

	B.P. by auscultation		B.P. by capacitance manometry	
Case	Initial pressure in mm Hg	Lowest pressure in mm Hg	Initial pressure in mm Hg	Lowest pressure in mm Hg
1.	132/86/80	65/?	134/78	68/32
2.	150/100/92	60/?	156/94	64/34
3.	122/72/64	68/40	118/68	65/40
4.	120/68/64	72/42	125/65	75/45
5.	142/92/84	58/?	138/85	60/30

THE RECOVERY OF THE BLOOD PRESSURE

The aim in induced hypotension is for the blood pressure to return gradually but steadily in the postoperative period. Patients should not leave the recovery room until they have absolute control of their airway, and a systolic blood pressure of over 85 mm Hg. The patient is kept flat in bed, and the foot of the bed is raised: when the pressure is consistently over 100 mm Hg systolic, the bed is cautiously levelled, although it may be required to be raised again, depending on the response of the blood pressure. Under such control, provided that an overdose of hexamethonium has not been given, the pressure returns smoothly over a period of a few hours. In this respect also, it was found preferable to give one or two effective doses of hexamethonium at the beginning of the hypotensive period, rather than to keep repeating small doses throughout the operation. The return of the blood pressure frequently (in nearly 75 per cent of cases) occurred in a series of steps, a typical case being shown in figure 2.

If the blood pressure did not show any signs of returning to normal levels after 2-2½ hours in the ward, a pressor agent was used. Any sympathomimetic amine will raise such lowered pressures and the most logical one to use would be l-noradrenaline; this drug, however, is short acting and must be given by continuous intravenous infusion, with very frequent control of the drip-rate by serial blood pressure determinations. Methylamphetamine has been used (Enderby, 1951; Shackleton, 1951; Rollason, 1952), but it has the disadvantage of being a cortical stimulant; moreover, methylamphetamine produces a substantial increase in force of the heart beat thereby increasing the work of the heart (Cotten *et al.*, 1954). Neither of these undesirable properties is shown by neosynephrine which has an action lasting up to 50 minutes in hypotensive cases; it is

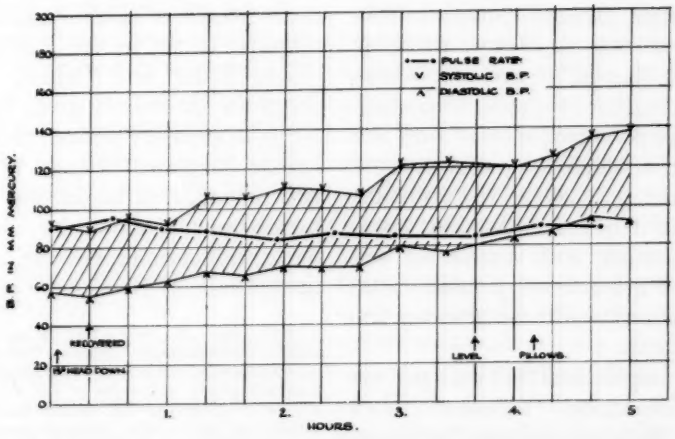


FIG. 2

The recovery phase of the blood pressure in the postoperative period, showing the control of posture, and the " step " return of the blood pressure.

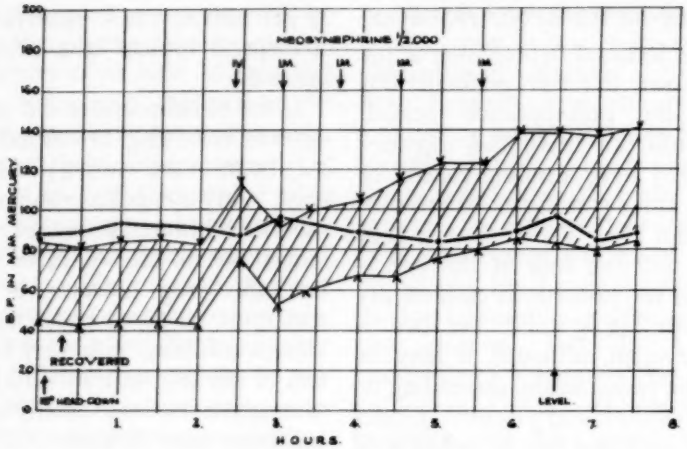


FIG. 3

Case showing delayed recovery of the blood pressure after induced hypotension, and the use of dilute solutions of neosynephrine to raise the pressure. Note the continued control of the position of the patient during this period.

a potent vasopressor, with only slight action on the cerebral cortex or on the cardiac automatic and muscular tissues. Since the aim is to produce a gradual rise in pressure any pressor drug must be given in sufficiently small dosage to avoid an abrupt and extreme pressure rise, because the normal autonomic damping mechanism to changes in pressure is suppressed by ganglion blockade. Neosynephrine is supplied in ampoules of 1 ml of 1 per cent solution, which is too concentrated for this purpose. 1/1,000 to 1/2,000 dilution was found to be satisfactory for intramuscular injection, and the use of this drug for raising the blood pressure after induced hypotension with hexamethonium is shown in figure 3.

It must be emphasized that such pressor drugs are not strictly antidotal: they merely raise the blood pressure but do not reverse the ganglion blockade, so that even with a rising blood pressure under these conditions, vasomotor control is still much diminished, and such patients must still have their posture rigidly controlled until convincing evidence of vasomotor control is manifested. Furthermore, analgesics such as morphine and pethidine increase the incidence of cardiovascular collapse in response to tilt in the normal individual (King, Elder and Dripps, 1952); such drugs are commonly given at this time in the postoperative period, thereby increasing the dangers of changes in posture. The adverse effect of neglecting these recommendations is shown by considering the one complication involving cardiovascular disturbance in the author's personal series.

Male, aged 28: first stage thoracoplasty under induced hypotension; result "excellent". Blood pressure on return to the ward 85/40 mm Hg; awake and responsive: when flat in bed, with 10° head down tilt, 95/45 mm Hg; two hours later, blood pressure 80/40 mm Hg. After 1/4,000 neosynephrine, 1 ml intravenously, blood pressure 100/60 mm Hg: 1/2,000 neosynephrine, 2 ml given intramuscularly every 30 minutes. When the blood pressure was 118/70 mm Hg, he was abruptly propped up, contrary to written

instructions: in spite of "feeling bad", he was maintained in this position for 15 minutes. The blood pressure was then 70/? mm Hg and he was immediately lowered and the foot of the bed raised; after intravenous neosynephrine his blood pressure was 100/60 mm Hg. There followed a gradual return of vasomotor control and at 5 hours postoperatively he was able to be half propped up, at blood pressure 118/76 mm Hg. He looked pale with a tachycardia and irregular rhythm. E.C.G. showed auricular fibrillation, but no evidence of cardiac infarction. He was later digitalized and improved. There was spontaneous conversion to auricular flutter four days later: the digitalis was stopped and he was put on quinidine with no effect. There was later spontaneous reconversion to fibrillation and digoxin therefore was recommenced. On the 24th day, his second stage operation was performed without incident under general anaesthesia, and a normal cardiac rhythm reappeared three days later. Frequent E.C.G. records showed no evidence of cardiac infarction at any stage.

In retrospect, this case showed that too large a dose (60 mg) of hexamethonium was used, bearing in mind that the lateral jack knife position, one of the most effective hypotensive positions, was being employed, and that, in spite of a satisfactory level of blood pressure after the pressor agent when flat, this patient's lack of ability to respond to being propped up abruptly, was due to the remaining ganglionic blockade. A low level of blood pressure resulted, and produced the disturbance of cardiac rhythm, although no evidence of more serious cardiac damage could be found. It is perhaps true to say that inadequate postoperative supervision, for whatever reason, is one of the strongest contra-indications to induced hypotension.

REMAINING PRESSOR RESPONSES AFTER HEXAMETHONIUM

The patient under induced hypotension with hexamethonium is very sensitive to the action of endogenous sympathetic hormone, as figures 4 and 5 show clearly. In these cases there was severe manipulation of the adrenals. There was an immediate sharp and severe rise in the blood pressure, the "pressor overshoot". Hexamethonium blockade eliminates the compensating mechanisms which normally come into play when changes of blood pressure occur, and which tend to oppose the direction of change. Thus under hexamethonium the rise in blood pressure and heart rate due to the release of adrenal medullary secretions assumed an exaggerated form. There was moreover a slight "overfall" as the effects of the adrenal stimulation wore off. Enderby (1952) has suggested that endogenous adrenaline may play a part in preventing the fall in blood pressure and in producing a tachycardia after hexamethonium in some of the younger patients. On the other hand, such patients often have a strong hypotensive response to intravenous procaine, as shown in figure 6, and Mason and Pelmore (1953) find that procaine, or more usefully, procaine amide, may be employed as an adjunct to hexamethonium in resistant young adults.

Figure 7 shows a patient under induced hypotension with a pressor overshoot response to acute anoxia. In this case, the oxygen supply ran out without being observed, until the deep cyanosis of severe anoxia was seen. The immediate cutting-in of the spare cylinder rapidly restored oxygenation, and, as can be seen, in a short time, the blood pressure and pulse rate fell, the former to below its original hypotensive level. The mechanism of this response is not quite clear. Purdo, Rennick and Moe (1950) showed that T.E.A. failed to block sympathetic inotrophic and chronotrophic effects on the atrioventricular node and ventricles of the dog, and concluded that these impulses must reach

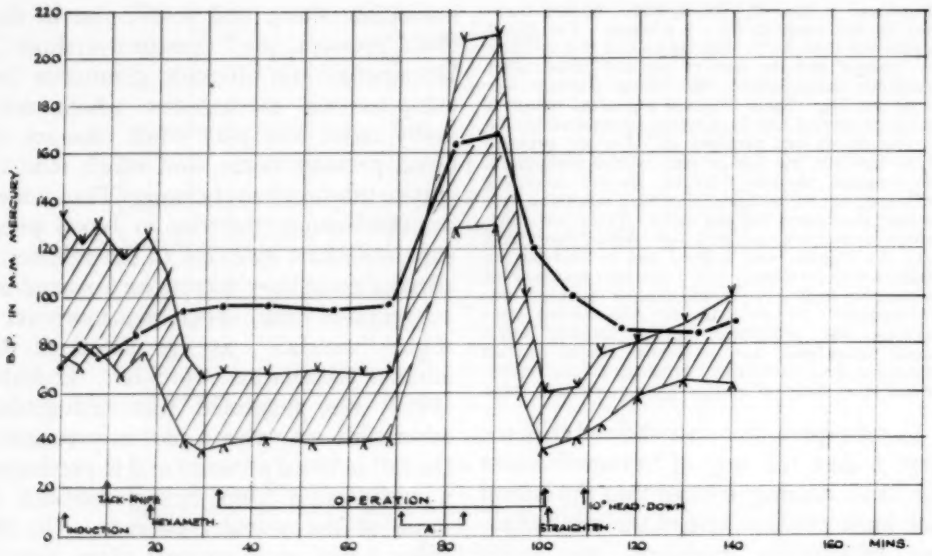


FIG. 4

Man, aged 42. Right nephrectomy. "Excellent" result, until the upper pole, which was very difficult to mobilize, was severely handled at "A". There was a violent pressor response with a high tachycardia. After the manipulation, the blood pressure fell to below its original hypotensive level (necessitating a change of posture); the pulse rate also returned to slightly below its previous level. This patient had a well compensating response to the assumption of the lateral jack-knife position under light anaesthesia.

the heart either without synaptic transmission or over synapses unresponsive to the action of T.E.A. The same considerations might apply to the anoxic pressor response after hexamethonium in humans, although hexamethonium does abolish the cold pressor response, and inhibits the vasopressor overshoot after the Valsalva manoeuvre (Finnerty and Freis, 1950). More probably, the adrenal glands themselves may be directly stimulated by the anoxic blood reaching them. Further investigation in man is obviously precluded although it is interesting to note that Van Bergen *et al.* (1954) produced hypoxia in one patient under induced hypotension with hexamethonium, by reducing the oxygen tension of the inspired gases to 80 mm Hg (corresponding to 10 volumes per cent) for four minutes. These workers found that the arterial pressure fell even further and that the heart rate rose. Following the administration of pure oxygen in this case, the pressure rose to its previous level, and they concluded that after hexamethonium blockade neither hypoxia nor hypercarbia produces its usual pressor response because the sympathetic effectors are blocked at their synapses. Certainly either hypoxia or hypercarbia before the injection of hexamethonium exaggerates the depressor response because of the presence of an increase in sympathetic tonus (Paton and Zaimis, 1951), but it may be that after hexamethonium blockade, the degree of

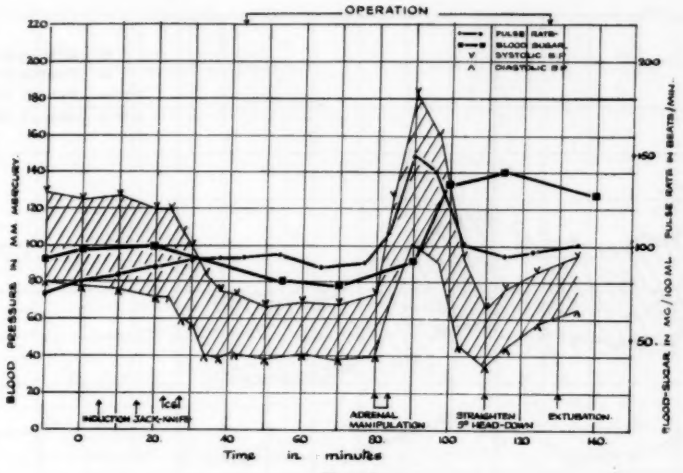


FIG. 5

Man, aged 45. Left nephrectomy. Recording of the blood pressure, pulse rate, and the venous blood sugar. At the 80th minute, severe adrenal manipulation was carried out. The blood pressure and pulse rate showed very similar changes to those in figure 4, including a slight "overfall" of pressure. The blood sugar fell slightly after hexamethonium, rose sharply after the adrenal manipulation, and remained at a somewhat higher level than before the administration of hexamethonium. The changes in blood sugar after the manipulation lag behind the changes in blood pressure and pulse rate.

oxygen-lack conditions whether the blood pressure falls further, or shows a violent pressor overshoot. It will be noted that there is a slight initial depressor effect in the case in figure 7, before the high blood pressure rise.

Support for the adrenal stimulation theory, in which adrenaline rather than noradrenaline would be released, is received by noting that the pressor response in the anoxic case was accompanied by a sharp tachycardia, which rapidly subsided when oxygenation was restored. This same type of tachycardia was seen in both cases of adrenal manipulation. Moreover, in the case in figure 5, venous blood sugar estimations (by the method of Fujita and Iwatake, 1931) were made. The blood sugar fell slightly after the administration of hexamethonium, as has been shown elsewhere (Griffiths, 1953b), but rose sharply after the adrenal manipulation, although lagging somewhat behind the rise in blood pressure and pulse rate; nor did it return quickly to its previous value as did the cardiovascular functions.

SUMMARY

During work on a series of cases of induced hypotension with hexamethonium under general anaesthesia, the following circulatory aspects were investigated:

(1) The bleeding time was determined by a "Modified Ivy" method. In 50 males the bleeding time was slightly increased under hypotension, but not more than in 50 similar cases under the same method of anaesthesia without hypotension. Five

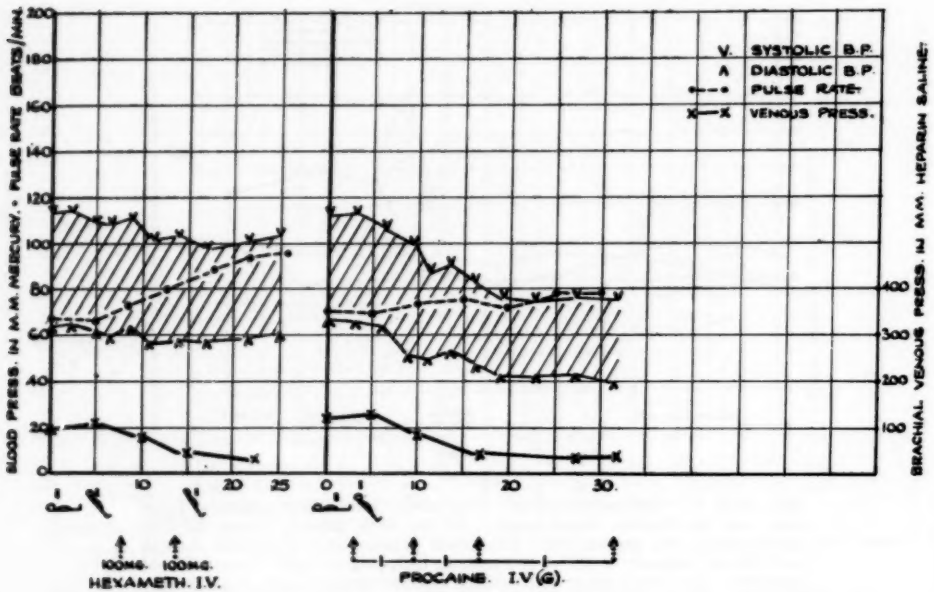


FIG. 6

Male, aged 22, showing responses to hexamethonium without and with procaine, at two different operations. In spite of a very steep foot-down tilt, and large doses of hexamethonium (200 mg) intravenously, there is only a slight and non-sustained response in the blood pressure, although there was an appreciable tachycardia. With intravenous procaine, however, the blood pressure was lowered, with the pulse rate remaining stable. The brachial venous pressure fell in both instances.

cases of reactionary haemorrhage out of 1,029 hypotensive cases are described.

(2) The circulation times (arm-respiratory centre and ankle-respiratory centre) under hypotension were determined. The arm-centre time was not altered by the induction of smooth anaesthesia, but was prolonged by the induction of hypotension although an increase in the foot-down tilt and in the hypotension did not result in any further alteration of the arm-centre time. By contrast, the ankle-centre time was similarly increased by hypotension, and was further increased by the use of an increased foot-down tilt. The theophylline-ethylenediamine test measured rates mainly in the venous side of the circulation, which was thus slowed by hypotension with hexamethonium, this effect being increased by gravitational pressure. There was no correlation between the degree of increase in the circulation time and the degree of hypotension.

(3) The blood pressure at hypotensive levels in five cases was measured by brachial intra-arterial capacitance manometry and the careful use of the mercury sphygmomanometer on the arm. The accuracy of the latter method at low pressures seemed to be clinically satisfactory.

(4) The recovery of the blood pressure in the postoperative period after induced hypotension is discussed, the use of neosynephrine as a pressor drug is des-

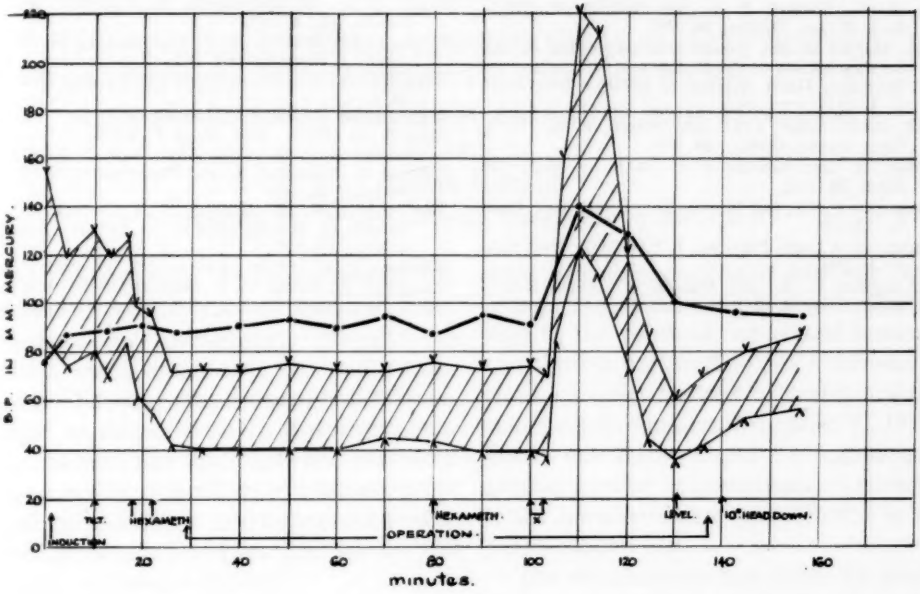


FIG. 7

Man, aged 41. Excision of rodent ulcer of face. At "X", acute anoxia supervened. There was a sharp pressure rise, and a pronounced tachycardia, preceded by a slight depressor effect. After full oxygenation was restored, the blood pressure fell to below its original hypotensive level, necessitating levelling the patient.

cribed, and stress is placed on the continued control of posture until the return of full vasomotor control.

(5) The remaining pressor responses under induced hypotension with hexamethonium to endogenous adrenal medullary secretion and to anoxia are illustrated and discussed.

ACKNOWLEDGMENTS

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THE INVESTIGATION OF CEREBRAL BLOOD FLOW DURING ANAESTHESIA WITH HYPOTENSION INDUCED BY THE USE OF HEXAMETHONIUM BROMIDE AND POSTURE

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THE consequences of anoxaemia to the cerebral cortical cells, ranging from psychopathic personality changes to idiocy, coma and death are well recognized. The fear that induced hypotension might at times result in this anoxaemia was the stimulus that made one overcome the technical difficulties of estimating the cerebral blood flow and endeavour to discover if the danger of cerebral anoxia was as real as it might appear.

Various papers and letters have been published of cases in which cerebral damage has occurred and been attributed to the hypotensive technique (Davison, 1951; Cropper, 1951; Bodman, 1952; Goldsmith and Hewer, 1952).

At the British Medical Association Conference at Cardiff in 1953, Davison stated that the main danger of induced hypotension was cerebral damage. The method was only justified when the operation was essential and could not easily be performed without a "bloodless field". At the same meeting Mushin stated that his hospital mortality rate was higher after hypotension and the deaths occurred mainly within the first two or three days after operation.

Hampton and Little (1953) showed from questionnaires sent to anaesthetists that in 21,000 cases of induced hypotension, 46 fatalities occurred of which 42 were probably associated with the technique. Non-fatal complications affecting mainly the cerebral, renal and coronary circulations occurred on 549 occasions. A similar inquiry showed 80 deaths in 6,805 patients (Annotation, *Brit. med. J.*, 1954). From this latter inquiry a significantly greater number of complications occurred if the blood pressure was allowed to fall below 80 mm Hg.

The first inquiry was from the results of 299 anaesthetists, and too much cannot be deduced from these results without adequate knowledge of the factors involved.

Nilsson (1953) used the "flicker-fusion" test of Berg on fifteen patients after operation. These patients had undergone a methonium induced postural hypotension. A positive reaction indicating cerebral injury, presumably anoxic in origin, was found in six of the cases. In the head-up position 5 out of 11 showed cerebral damage, whilst of four in the head-down position one showed cerebral damage. The difficulty of accepting this cerebral damage as being due to the effects of hypotension is that a control series was not performed under anaesthesia alone.

Gilmore *et al.* (1952) have shown that the circulation time is increased by the action of methonium and posture. In the aged who already have increased circula-

tion times this may lead to cerebral thrombosis. A case of this kind has been reported (*Anaesthesia*, **8**, 262).

Following a hexamethonium induced hypotension, Goldsmith and Hewer (1952) have reported a vascular ischaemia of the retina. The causes of retinal ischaemia are thrombosis or embolism of the retinal artery, pressure on the eye from without (as with an anaesthetic face-mask), increasing intra-ocular tension to a point where arterial circulation is mechanically impeded, arterial spasm and hypotension so low as not to maintain an adequate blood supply. This hypotension would, according to Fritz (1950), have to be below 25 mm Hg. The hypotension in the case reported was never below 70 mm Hg as recorded from the brachial artery during the operation, i.e. presumably at heart level. If Enderby's (1954) reasoning is accepted the blood pressure in the brain under these conditions might have been very near this critical level. There was a re-established normal blood flow within 24 hours which rules out thrombosis and embolism. Of the remaining causes the authors have suggested spasm, although they admit the connection with hexamethonium is obscure. I would prefer to think in terms of a too tightly fitting face-mask rather than too low a blood pressure or a combination of both.

Bodman (1952) reports the post-operative death of a man of 76 which could be related to the hypotension produced during operation. At the post-mortem examination cerebral softening was present with atheromatous narrowing of cerebral vessels.

It would seem inadvisable to lower the pressure in such an aged patient. However, Pelmore (1952) argues: "hexamethonium bromide may well have dilated, and temporarily relieved the diseased arterial circulation. Blood loss with an ordinary anaesthetic could easily have caused compensatory vasoconstriction and thrombosis during the operation." This accumulation of clinical evidence indicates that there are greater dangers during anaesthesia with a low blood pressure than with a normal blood pressure. It was felt necessary to carry out the present investigation to determine how great was the danger of cerebral hypoxia and what, if any, limitations should be placed upon the lowering of blood pressure during anaesthesia.

METHOD ADOPTED TO ESTIMATE CEREBRAL BLOOD FLOW

The estimations of cerebral blood flow were made according to the original technique of Kety and Schmidt (1945, 1948; Kety, 1948) which involves the inhalation of a non-anaesthetic concentration of nitrous oxide for ten minutes and the removal during the period of timed samples of blood from the superior jugular bulb end and a peripheral artery. There was a small modification in that venous samples were taken from the lateral sinus and not the jugular bulb. This meant that the patients were limited to those undergoing mastoidectomy in whom the lateral sinus was exposed.

The nitrous oxide concentration in the samples was plotted against time and the integrated arterial-cerebral venous nitrous oxide difference

$$\left(\int_0^{10} (A\text{-}v)dt \right)$$

was calculated from the curves.

A cerebral venous blank was taken immediately before each estimation, i.e. prior to the inhaling of nitrous oxide, and five arterial and cerebral venous specimens during the ten-minute period of inhaling the nitrous oxide mixture. Arterial sampling was through an indwelling needle placed in either the brachial or femoral artery. The nitrous oxide mixture, which was supplied commercially (N_2O 15 per cent; O_2 21 per cent; N_2 64 per cent) was conducted to the cuffed endotracheal tube in the patient by way of a system incorporating an anaesthetic gauge giving a flow rate of 10 litres per minute, a reservoir bag and corrugated tubing with an expiratory and non-return valve. A cuffed endotracheal tube was used to prevent leakage and dilution of the gas mixture with air.

The blood samples were analysed for nitrous oxide content in a Van Slyke and Neill manometric apparatus according to the technique of Orcutt and Waters (1937) modified by Kety and Schmidt (1948).

Type of Case Investigated.

Patients undergoing mastoid operations in whom the lateral sinus was exposed.

Anaesthetic Procedure.

Premedication. Subcutaneous atropine 0.6 mg and pethidine 100 mg one hour before operation unless stated otherwise.

Induction was with thiopentone and suxamethonium and a large cuffed tube greased with 1 per cent cinchocaine cream inserted after the larynx and trachea had been sprayed with ¼ drachm (0.22 ml) of 2 per cent lignocaine.

Anaesthesia was maintained with a 0.4 per cent thiopentone intravenous drip.

Position of Patient. 10° foot-down tilt.

Estimations of Cerebral Blood Flow were carried out: (a) under anaesthesia; (b) under anaesthesia and after hypotension had been induced with hexamethonium for approximately 20 minutes.

A twenty-minute interval was allowed between the estimations to enable most of the nitrous oxide to be removed from the blood after the first estimation, and to allow time for the hypotension to become stationary. The cerebral venous blank specimen showed if there was any residual nitrous oxide. Hypotension was induced immediately after the first estimation by injecting hexamethonium in appropriate amounts.

The cerebral venous blood was obtained from the lateral sinus using sterile syringes which had been greased with liquid paraffin and heparinized. Immediately the blood was taken the needle mount was capped with a sealed needle hub, the syringe rolled to ensure adequate heparinization and placed on ice. The arterial samples were obtained from either the brachial or femoral arteries and were treated similarly to the venous samples. One per cent procaine was injected into and around the artery after the samples were taken to prevent spasm.

The mean cerebral blood flow (ml of blood per 100 g of brain per minute) was calculated from the formula:

$$\int_{o}^{t} \frac{100\ V}{(A\text{-}V)\ dt}$$

where V = the nitrous oxide content, in volumes per cent, of the cerebral venous specimen taken at the end of the tenth minute; (A-V)dt is the integral of the arterial-cerebral venous nitrous oxide

difference over the ten-minute period determined from the difference between the nitrous oxide contents of the two integrated specimens.

Arterial blood pressure was measured by the auscultatory method in the arm before, during and after each estimation of blood flow.

METHOD USED TO ESTIMATE CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCE

Samples of blood were obtained in heparinized syringes—the cerebral venous samples from the lateral sinus and the arterial samples from either the brachial or femoral artery. The choice of case was similar to those on whom cerebral blood flow estimations were made, but the method of anaesthesia differed. The method of anaesthesia for each case is given in table II.

The samples of blood were stored in test tubes under liquid paraffin and the oxygen content of the samples estimated by the colorimetric method (Exton *et al.*, 1945).

The error in the estimation of oxygen by this method may be in the order of ± 2 vol per cent, but as it was changes in the arteriovenous oxygen difference that were being sought, this error was less important, provided it was borne in mind. Also, as it was only arteriovenous oxygen difference results that were needed, the error due to the plasma oxygen content to some extent cancels itself out.

RESULTS

Cerebral Blood Flow Estimations.

The results are seen in table I.

The average cerebral blood flow in five patients during anaesthesia with a *normal blood pressure* was 48.3 ml per 100 g of brain per minute. The highest flow recorded was 68.3 ml and the lowest 26.0 ml, giving a range of 42.3 ml. This average figure for blood flow through the brain is lower than the one found by Wechsler, Dripps and Kety (1951) who gave 60.5 ml as their average. However, their figure was obtained with the patient lying horizontal with smaller amounts of thiopentone. The average for conscious patients is 54 ml ± 12 ml (Wright, 1952).

The average cerebral blood flow in six patients during anaesthesia with a *low blood pressure* was 33.5 ml per 100 g of brain per minute. The highest flow was 47.5 and the lowest 24.2, giving a range of 23.3 ml.

In four of the cases the cerebral blood flow was obtained before and during hypotension and in each case there was a fall in flow during hypotension, the fall ranging from 8.3 ml to 35 ml. From table I it appears that in these four cases the greater the fall in blood pressure, the greater is the fall in cerebral blood flow.

During the blood flow estimations the arteriovenous oxygen difference was obtained in four of the cases. The oxygen in the blood was estimated using the Van Slyke apparatus.

With a normal blood pressure the average arteriovenous oxygen difference was 4.0 vol per cent.

During hypotension the average arteriovenous oxygen difference was 5.7 vol per cent. The average systolic blood pressure was 75 mm Hg.

With a low blood pressure there was no change in arterial oxygen saturation except in one case. In this particular case the blood pressure was not very low as can

TABLE I

Table of cerebral blood flow estimations

No.	Age	Hb. and R.B.C.s	Blood pressure mm Hg	Arterial oxygen	C.V.O.	C.B.F.	Blood pressure	Arterial oxygen	C.V.O.	Total dose thiopentone g	Per cent drop in M.A.B.P.	C.B.F.
1	17	—	110/75	—	—	—	70/50	—	—	1.7	34	33.1
2	33	80% 4.1	130/65	10.6	8.5	—	78/60	10.7	6.1	1.5	30	33.3
3	20	92% 4.5	110/80	—	—	32.5	75/55	—	—	1.75	32	24.2
4	29	90% 4.5	140/100	—	—	58.1	60/45	—	—	2.0	57	29.5
5	17	90% 4.71	110/70	18.9	10.4	26.0	100/60	16.0	9.4	2.75	11	—
6	26	70% 3.7	120/80	14.9	12.4	56.7	80/50	14.6	10.7	2.0	35	47.5
7	25	93% 5.1	120/85	20.3	17.5	68.3	65/45	20.8	13.1	2.25	46	33.3
Average	24					48.3				2.0	35.0	33.5

Average arteriovenous oxygen difference:
before hypotension = 4.0; during hypotension = 5.7
Average fall in M.A.B.P. = 35 per cent
Average fall in C.B.F. = 31 per cent
Average systolic B.P. during hypotension = 75 mm Hg.

C.V.O. = Cerebral venous oxygen.
C.B.F. = Cerebral blood flow.
M.A.B.P. = Mean arterial blood pressure = diastolic blood pressure plus half the pulse pressure.

TABLE II

Changes in cerebral arteriovenous oxygen differences before and during hypotension. Chart of case details in each arteriovenous oxygen difference estimation.

Case	Sex	Age	Weight st	Weight lb	B.P. before C_6	Min of hypotension between samples	Per cent fall in M.A.B.P.	Mg of C_6	Degree of hypotension: Tilt (°)	Degree of hypotension: B.P. mm Hg	Reduction of cerebral venous 0_2 vol per cent	Change in arterial 0_2 saturation	Reduction in venous 0_2 in arm vein	Anaesthetic given	
* 1	M	32	10	3	135/85	10	25.54	50	20	100/65	0.2	−0.8		T.N_2O.P.E.	*ST*
2	M	34	10	2	120/90	10	31.4	100	20	80/65	0.6	+0.1		T.N_2O.G.P.E.	*ST*
3	M	50	8	12	120/90	5	42.9	50	20	70/50	0.2	+0.1		EC.E.N_2O.	*ST*
4	M	23	11	6	120/80	10	35.0	200	20	75/55	0.4	−0.1		T.N_2O.G.P.E.	*ST*
5	M	21	10	6	115/90	10	31.4	180	20	80/60	0.7	+0.4		T.N_2O.G.P.E.	*ST*
6	M	53	7	3	145/90	25	31.4	100	20	85/70	1.6	No change		T.N_2O.G.E.	
7	M	63	8	9	140/100	17	35.7	90	20	80/70	3.1	−0.2		T.N_2O.S.E.	*ST*
8	M	47	11	0	120/90	15	38.1	50	10	70/60	1.3	−0.5		T.N_2O.S.TR.	
9	F	24	8	7	115/90	15	43.9	100	10	60/50	0.9	−0.3	−0.9	T.N_2O.S.P.TR.	
*10	M	18	10	0	115/85	15	35.0	50	10	75/55	1.9		−1.3	T.N_2O.S.P.TR.	
*11	F	28	8	0	110/75	25	—	90	10	80/55	0.8	No sample	−0.7	T.N_2O.S.P.TR.	
12	M	37	12	6	125/95	15	39.1	100	10	75/60	No change	+0.2		T.N_2O.S.P.E.	
13	F	21	8	0	120/90	15	36.2	100	10	70/55	0.6 inc.	+0.4	0.3 inc.	T.N_2O.S.E.	
*14	F	23	8	1	115/85	20	—	150	10	110/85	0.8	No sample	−0.7	T.N_2O.S.P.E.	
15	M	20	11	4	110/80	15	34.7	150	10	70/55	1.4	+1.0	−0.6	T.N_2O.S.P.E.	
*16	M	18	10	0	130/90	22	4.5	150	10	120/90	0.2 inc.	−0.1	−0.6	T.N_2O.S.P.E.	

(*Not included in results)
Average fall in M.A.B.P. = 36.2 per cent
ECG recordings in cases 2, 3, 5, 6, 7.
In Cases 2 and 5 in the youngest age group no change in ECG.
In Cases 3, 6 and 7 in the over-50 age group depression of the ST segment with QRS spread with hypotension. ? Suggestive of myocardial anoxia.

T = Thiopentone
N_2O = Nitrous oxide
S = Suxamethonium
P = Pethidine
E = Ether
EC = Ethyl chloride
G = Gallamine triethiodide
TR = Trichlorethylene
ST = Spirometer tracing

be seen from the table, but the amount of thiopentone administered was larger than normal. The suggested explanation is that there was respiratory inadequacy.

The arteriovenous oxygen difference was increased in every patient during hypotension.

ESTIMATION OF CEREBRAL VASCULAR RESISTANCE

The cerebral vascular resistance could be estimated in only four cases before and during hypotension because of incomplete data.

$$\text{C.V.R.} = \frac{\text{M.A.B.P.}}{\text{C.B.F.}}$$

C.V.R. = Cerebral vascular resistance.

M.A.B.P. = Mean arterial blood pressure = Diastolic pressure plus half the pulse pressure.

C.B.F. = Cerebral blood flow.

Case No.	C.V.R. before hypotension	C.V.R. during hypotension
3	2.9	2.7
4	2.1	1.6
6	1.7	1.4
7	1.6	1.5
Average	2.2	1.8

In each estimation the cerebral vascular resistance is shown to be decreased. This decrease in resistance was not great enough to maintain the blood flow through the brain (with a lowered blood pressure) at the same level as the blood flow with a normal pressure.

ARTERIOVENOUS OXYGEN RESULTS

Using Exton's method of estimating oxygen concentration. Cases not included in the arteriovenous oxygen estimation.

Case No. 1, Case No. 16 — No real degree of hypotension obtained.

Case No. 10, Case No. 11, Case No. 14 — No arterial samples obtained.

Results of the remaining eleven cases.

Without hypotension the average arteriovenous oxygen difference = 3.5 (±0.98) vol per cent.

With hypotension = 4.2 (±1.16) vol per cent.

The average increase in arteriovenous oxygen difference is 0.7 (±0.12) vol per cent (not statistically significant).

There is no significant change in arterial oxygen saturation during hypotension. It would not be expected as the respiration should be unaffected.

During hypotension the average systolic pressure was 74 mm Hg (the least fall being to 85 mm Hg and the greatest fall to 60 mm Hg) and the concentration of oxygen inhaled in the anaesthetic mixture was 25 per cent.

Saunders (1954) obtained a figure of 4.8 vol per cent with an average systolic pressure of 54.5 mm Hg and inhaling a mixture containing 80 per cent oxygen.

Wechsler *et al.* (1951) estimated the cerebral arteriovenous oxygen difference under thiopentone anaesthesia without hypotension to be 3.7 vol per cent. The average amount of thiopentone used in each case in their series was 0.93 g. The average amount of thiopentone used in the present series was about 0.5 g.

TABLE III

Arteriovenous oxygen difference results using Exton's colorimetric method of estimating blood oxygen

No.	Age	Effect of hypotension on A-V.O_2 difference			Change in arterial oxygenation		Change in arm vein		Change in lateral sinus		Time of hypotension between samples (min)
		Before	After	Increase	Before	After	Before	After	Before	After	
* 1	32	6.5	5.9	(Dec.) 0.6	17.8	17.0	No real hypotension		11.3	11.1	10
2	34	3.9	4.6	0.7	17.7	17.8			13.8	13.2	10
3	50	4.3	4.6	0.3	16.9	17.0			12.6	12.4	5
4	23	2.4	2.7	0.3	15.2	15.1			12.8	12.4	10
5	21	1.9	3.0	1.1	12.8	13.2			10.9	10.2	10
6	53	2.2	3.8	1.6	17.0	17.0			14.8	13.2	25
7	63	5.2	7.1	1.9	12.0	11.8			7.8	4.7	17
8	47	3.8	4.6	0.8	14.3	13.8			10.5	9.2	15
9	24	4.2	4.8	0.4	14.5	14.2	10.1	9.2	10.3	9.4	15
*10	18	Possibly venous			12.2	11.3	11.5	10.2	10.8	8.9	15
*11	28	No arterial samples			(11.2 venous	10.5)	11.2	10.5	8.3	7.5	25
12	37	4.5	4.7	0.2	15.0	15.2			10.5	10.5	15
13	21	2.1	2.4	0.3	13.4	14.3	11.6	11.9	11.3	11.9	15
*14	23	No arterial samples			(12.7 venous	13.0)	13.3	13.0	10.9	10.1	20
15	20	3.7	4.1	0.4	14.4	13.4	10.1	9.5	10.7	9.3	15
*16	18	3.7	3.4	(Dec.) 0.3	15.2	15.1	No hypotension		11.5	11.7	22

* = Cases not included in results.
" Before " = Before hypotension with posture (*see* other table for degree of posture).
" After " = After hypotension has been induced with hexamethonium. Posture same as in " Before ".

DISCUSSION OF RESULTS

There has been a large amount of experimental data published in recent years on the physiology of the circulation of the brain (Annotation, *Lancet*, 1954). The work performed between 1938 and 1948 has been tabulated in *Physiological Reviews* (1952).

(1) *Cerebral Blood Flow.*

The effect of lowering the blood pressure on the cerebral circulation in hypertensive patients has been studied by Kety *et al.* (1948; 1950), by means of a differential spinal block. The cerebral vascular resistance might be expected to be reduced coincident with a fall in arterial blood pressure. Despite the expected decrease in cerebral vascular resistance the cerebral blood flow fell during the hypotensive period. The explanation suggested by Kety for this result is that a differential spinal block only induces dilatation in the vascular bed of the region blocked and only indirectly affects the circulation through the brain.

The work of Harmel *et al.* (1949), however, suggests that the sympathetic plays little part in the regulation of cerebral blood flow. They observed the effect of a bilateral stellate ganglion block on the cerebral blood flow in normotensive and hypertensive individuals and found there was no change in cerebral blood flow or cerebral vascular resistance before or after stellate ganglion block in 13 patients.

The effects of a cerebral vasodilator as well as a general vasodilator drug have

been studied by Hafkenschiel *et al.* (1950). They studied the use of dihydroergocornine on the cerebral blood flow in normotensive patients. There were slight but insignificant decreases in the cerebral blood flow, cerebral vascular resistance and cerebral metabolic rate, despite the fact that the mean arterial pressure was significantly reduced. They interpreted their results as follows: "The unchanged oxygen content of the internal jugular venous blood is an indication that the slight decrease in resistance of the vessels of the normotensive brain may be sufficient to prevent a marked decrease in cerebral blood flow and consequently decrease in cerebral oxygen tension, since cerebral blood flow and oxygen uptake are maintained essentially unchanged in the face of a 17 per cent fall in mean arterial pressure induced by dihydroergocornine."

It seems unlikely from the work of Harmel with stellate ganglion blocks that hexamethonium will lower the cerebral vascular resistance by means of a sympathetic block. However, such relaxation may occur from a drop in systemic arterial blood pressure as suggested by the use of a differential spinal block and the use of dihydroergocornine.

That there is cerebrovascular relaxation sufficient to maintain an adequate cerebral blood flow and oxygen consumption despite the fall in blood pressure of the order obtained with hexamethonium to provide a relatively bloodless operation site is suggested by the results of the work in this paper.

In patients with essential hypertension the cerebral vascular resistance is shown to be increased when estimated by cerebral blood flow measurement (Kety *et al.* 1948). The effect of hexamethonium on six hypotensive unanaesthetized patients has been studied by Dewar *et al.* (1953a). The mean arterial blood pressure fell by an average of 30 per cent but no significant change occurred in mean cerebral blood flow. The cerebral vascular resistance was decreased by 28 per cent and the rate of cerebral oxygen utilization showed no essential alteration.

Histamine has been shown to be an effective cerebral vasodilator, although it produces no concomitant increase in the mean cerebral blood flow (Shenkin, 1951; Alman and Rosenberg, 1952). Both Alman and Rosenberg and Kety (1950) considered that the failure of histamine to increase the cerebral blood flow was most probably the result of the fall in arterial pressure produced by it. Shenkin (1951) analysed his figures relative to this point and found that the response of the cerebral blood flow varied with the degree of alteration in the head of pressure; where the fall in mean arterial blood pressure averaged 23 per cent, the flow was not materially affected, whereas increases and decreases respectively occurred with falls in mean arterial blood pressure averaging 12 per cent and 50 per cent. Some of these results on the correlation between the changes in cerebral blood flow and mean arterial blood pressure have been confirmed by Dewar *et al.* (1953b), who investigated the effect of tolazoline hydrochloride ("Priscol") on blood pressure. The average decrease in mean arterial blood pressure of six patients was 6 per cent whilst increases in cerebral blood flow averaged 25 per cent. The patients had mitral stenosis and their average age was 33 years. Using patients in the older age

group, Scheinberg *et al.* (1953) did not observe any change in cerebral vascular resistance.

Saunders (1954) reduced the blood pressure in conscious humans to 60 mm Hg with hexamethonium given with the subjects in the erect position. All of them tolerated these conditions for five minutes without losing consciousness. Electroencephalographic evidence in the conscious subject suggests 55 mm Hg is a critical level (Bromage, 1953).

Morris and Moyer (1953; 1954) have observed a consistent reduction in cerebral blood flow in the non-anaesthetized patient when the blood pressure was reduced with hexamethonium. Cerebral anoxia was prevented in these patients by an increased oxygen extraction ($(A\text{-}V)O_2$ difference increased) from the blood flowing to the brain unless the mean blood pressure was reduced below 55 mm Hg. Below this level the calculated cerebral oxygen uptake per minute was occasionally reduced, though this was not constant.

These results of Morris and Moyer in the non-anaesthetized subject are similar to the results obtained in the present investigation on anaesthetized patients. All the patients in the present series showed a fall in blood flow through the brain with a decrease in blood pressure, but, as this series consisted of only four patients in whom cerebral blood flow was measured before and during hypotension, I feel a greater number of estimations are necessary for confirmation of my results. This is especially so in view of the conflicting literature already published on this subject.

These results were all in the younger age group and do not necessarily apply to older people. In fact in older people, with their already diminished cerebral blood flow, it would appear, from the work of Clarke *et al.* (1954) using a vasodilator drug, to be rather hazardous to lower the blood pressure.

The effect of the reduction in cerebral blood flow with a head-up tilt in the present series is dealt with in the discussion on cerebral metabolism where the results are correlated with the arteriovenous oxygen difference.

(2) *Arteriovenous Oxygen Differences.*

By re-arranging the Fick formula for oxygen uptake by the brain, the following equation emerges:

$$(A\text{-}V)O_2 = \frac{(CMR)O_2}{C.B.F.}$$

The reciprocal of the cerebral arteriovenous oxygen difference ($(A\text{-}V)O_2$) represents a useful concept; the ratio of cerebral blood flow (C.B.F.) to metabolic demand ($CMRO_2$). Thus an increase in arteriovenous oxygen difference signifies a decrease in the ability of the cerebral circulation to meet the metabolic needs of the brain, even though it conveys no information with respect to either blood flow or metabolism separately. The arteriovenous oxygen difference can thus be used with this understanding as an inverse measure of the sufficiency of the cerebral circulation.

Saunders (1954) found in eight patients during anaesthesia with an average systolic pressure of 52 mm Hg that the average cerebral arteriovenous oxygen difference was 4.8 vol per cent. This hypotension was obtained with hexamethonium and negative pressure applied to the lower limbs (Saunders, 1953) and

with the patient horizontal. The figure given for cerebral arteriovenous oxygen difference during normal anaesthesia is 3.7 vol per cent (Wechsler *et al.*, 1951).

Saunders' figure of 4.8 vol per cent is an increase over the normal figure during anaesthesia of 3.7 vol per cent, and this suggests a decreased ability of the cerebral circulation to cope with the oxygen requirements of the brain. If on the other hand there is a decreased blood flow through the brain this increased arteriovenous oxygen difference may be sufficient to compensate for the decreased flow and thus leave the actual oxygen uptake unchanged (Hughes and Riddle, 1954).

In the present investigation the arteriovenous oxygen difference is increased during hypotension induced with hexamethonium during various methods of anaesthesia and using two different methods of estimation. This suggests that the cerebral circulation is less adequate with regard to the demands that may be placed upon it. This is borne out by the estimation of cerebral blood flow which decreases during hypotension, when compared with the cerebral blood during normal anaesthesia.

However, there does not appear to be any danger of cerebral hypoxia in this series of patients undergoing cerebral blood flow estimations as the arteriovenous oxygen difference increases sufficiently to give the same figure for cerebral oxygen uptake under these conditions of hypotension as during normal anaesthesia.

(3) *Cerebral Metabolism.*

The differences in oxygen content of the blood entering and leaving the brain depend on:

(i) Rate of oxygen consumption by the brain;

(ii) Amount of blood flow through the brain.

The brain metabolism is proportional to the oxygen consumption. If the metabolism is constant, then the blood flow is proportional to the arteriovenous oxygen difference. For this statement to be true during anaesthesia with an induced hypotension the cerebral metabolic rate will have to be measured before hypotension and during hypotension and found to be unchanged. Then any changes in the arteriovenous oxygen difference will suggest changes in blood flow.

Saunders (1952) has estimated the cerebral venous oxygen content at arterial pressures of 60 mm Hg or less and he suggests that the results indicate that cerebral vasodilatation very nearly compensates for the fall in arterial pressure, so that under the conditions used by him, cerebral anoxia does not occur. I replied as follows (Hughes, 1952): "Assuming there is no difference in cerebral oxygen metabolism during anaesthesia before hypotension and during hypotension, then provided there is sufficient vasodilatation to compensate for the reduction in flow, cerebral functional activity will be unchanged, but once the limit of this type of compensation has been reached and the oxygen uptake by the brain falls, then cerebral anoxia will ensue. This critical level of hypotension will obviously vary with the amount of vasodilatation each individual is capable of and is a factor impossible to assess with any degree of accuracy."

From the formula:

$$CMR(O_2) = CBF \times \frac{(A\text{-}V)O_2}{100}$$

I suggested (Hughes, 1954) that when there is too great a fall in cerebral blood flow and the arteriovenous oxygen difference does not increase sufficiently, the formula will show a decreased cerebral metabolic rate. I suggested that there is no valid reason to expect a decrease in cerebral metabolism under these conditions of hypotension and such a reduction may indicate cerebral anoxia.

However, Sancetta *et al.* (1952) have demonstrated a fall in total body consumption of oxygen in patients with hypotension following a spinal anaesthetic. There was no correlation between the fall in blood pressure and the fall in oxygen consumption. The fall in oxygen consumption was about 10 per cent which the authors partly ascribed to the removal of muscle tone and the association of decreased metabolic rate with hypotension.

Another factor according to Payne and Beswick (1954) accounting for the reduction in metabolism may be the prevention of the neurogenic secretion of adrenaline. In their work on cats, these workers found that the diminution in oxygen consumption produced by hexamethonium was of the same order as that produced by spinal anaesthesia, and they suggest that decrease in oxygen consumption is brought about by a similar mechanism namely the diminution in the secretion of adrenaline.

Anaesthesia with thiopentone alone with only a mild degree of hypotension (mean arterial blood pressure of 71 mm Hg as compared with the normal 85 mm Hg) reduces the cerebral metabolic rate when expressed as millimetres of oxygen per 100 g of brain per minute by about 40 per cent (Wechsler *et al.*, 1951).

In patients with cerebral tumours the brain metabolism is little affected until the intracranial pressure reaches about 400 mm of water; there is then a consistent fall in cerebral blood flow, associated with a diminished cerebral metabolic rate of oxygen, and the onset of mental symptoms, usually coma (Kety *et al.*, 1948).

In patients with arteriosclerosis the cerebral metabolic rate of oxygen is reduced as is also the cerebral blood flow when compared with the figures for healthy young men.

The Estimation of Cerebral Metabolic Rate using the Results obtained in the Cerebral Blood Flow Estimations.

In this series of patients cerebral blood flow decreased with a lowered blood pressure. Also in this series the arteriovenous oxygen difference increased with a fall in blood pressure. In all these cases anaesthetic maintenance was with thiopentone alone.

The oxygen uptake by the brain before and during hypotension can be calculated from these figures using the equation:

$$(CMR)O_2 = CBF \times \frac{(A\text{-}V)O_2}{100}$$

Method I. Using the average figures given in table I.

During anaesthesia with a normal blood pressure:

Average CBF = 48.3

Average $(A\text{-}V)O_2 = 4.0$

$$\therefore (CMR)O_2 = \frac{48.3 \times 4}{100}$$

$$= 1.9 \text{ ml oxygen per } 100 \text{ g of brain per min.}$$

During anaesthesia with hypotension:
Average CBF = 33.5
Average $(A\text{-}V)O_2 = 5.7$

$$\therefore (CMR)O_2 = \frac{33.5 \times 5.7}{100}$$

= 1.9 ml oxygen per 100 g of brain per min.

Method II. Using the above equation the $(CMR)O_2$ is estimated in each case.

The average $(CMR)O_2$ obtained by this method does not include as many results as the first method, as $(CMR)O_2$ could not be estimated in all the cases because of lack of information as to either the CBF or the $(A\text{-}V)O_2$ difference.

The cerebral oxygen consumption in each case is shown in the following table:

Case No.	$(CMR)O_2$ during normal anaesthesia	$(CMR)O_2$ during anaesthesia with a low blood pressure
2	—	1.5
5	2.2	—
6	1.4	1.9
7	1.9	2.5
Average	1.83	1.97

The mean results for oxygen consumption by the brain are practically identical. Furthermore in the individual cases the difference in oxygen consumption between the two results is within the experimental error of the method (Kety *et al.*, 1948).

There is no decrease in oxygen uptake by the brain suggesting that the arteriovenous difference has increased sufficiently to compensate for the decreased cerebral blood flow and thus any cerebral hypoxia is prevented.

Wechsler *et al.* (1951) estimated $(CMR)O_2$ with thiopentone anaesthesia to be 2.1 ml oxygen per 100 g brain per minute. (Average amount of thiopentone used was 0.93 g.) In the present series the average amount of thiopentone used was 2.0 g in those cases in which CBF was estimated.

CONCLUSIONS

Changes in the cerebral circulation have been assessed by noting alterations in the gaseous content of the blood entering and leaving the brain.

(A) The blood flow through the brain falls during hypotension of the order used in this series. Thus vasodilatation of cerebral vessels cannot completely compensate by decreasing the resistance to flow.

(B) This decrease in cerebral blood flow was not sufficient to cause any diminution in the oxygen uptake by the brain. This suggests that there was no oxygen want.

(C) Provided there is no depression of respiration and sufficient oxygen is available to the patient the arterial oxygen saturation will be unchanged.

The Bearing of the Results on the Management of Induced Hypotension.

(A) The hypotension should never be more than is necessary for the success of the operation. The greater the hypotension the greater the dangers of cerebral anoxia.

(B) The method should not be used when there is any ventilatory inadequacy or when the oxygen carrying power of the blood is reduced.

(C) People in the older age group are unsuitable subjects because of the increased danger of cerebral anaemia and thrombosis.

(D) It is interesting, though irrelevant to this paper, that hypothermia reduces cerebral metabolism, according to the work of Fazekas *et al.* (1939) on dogs. Thus it would appear that, as there may be a danger during excessive lowering of blood pressure of oxygen want by the brain, the combination of ganglionic blocking drugs with hypothermia would be a safer procedure (Delorme, 1952; Learmonth, 1953).

SUMMARY

There is little information available on the haemodynamics of the cerebral circulation in normotensive anaesthetized individuals who suffer a severe reduction in blood pressure.

A reduction in blood pressure has been obtained in anaesthetized patients by using hexamethonium bromide and posture. The clinical evidence of cerebral damage that has appeared in the literature following the use of the method is discussed. The literature on the changes in cerebral blood flow is reviewed.

The cerebral blood flow has been estimated during anaesthesia using the nitrous oxide method with a normal blood pressure and with an induced hypotension. The cerebral blood flow shows a decrease with a lowered blood pressure whilst there is an increase in the arteriovenous oxygen difference. From the results, the uptake of oxygen by the brain during anaesthesia with a normal blood pressure and with a lowered blood pressure have been calculated and show no significant difference. The cerebrovascular resistance, however, is shown to be decreased during hypotension.

The arteriovenous oxygen results have been confirmed in another series of cases using Exton's method for the estimation of oxygen. The conclusions drawn are:

(1) The decreased cerebrovascular resistance is not sufficient to maintain the cerebral blood flow.

(2) The decreased cerebral blood flow is compensated by an increased arteriovenous oxygen difference which appears to be sufficient to maintain the cerebral uptake of oxygen.

(3) In the light of our present knowledge it would be unwise to subject patients over fifty to a prolonged hypotension of this nature and even in younger people it should be reserved for those cases in which it is essential to the success of the operation.

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THE EFFECTS OF NISENTIL HYDROCHLORIDE AND LEVALLORPHAN TARTRATE ON CEREBROSPINAL FLUID PRESSURE

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A KNOWLEDGE of the effects of anaesthetic agents on the cerebrospinal fluid (C.S.F.) pressure is of considerable importance to the anaesthetist especially in relation to anaesthesia for neurosurgery.

HISTORICAL

Gardner and Lamb (1931) reported that rectally administered anaesthetic doses of bromethol caused an increase in C.S.F. pressure. Later Finesinger and Cobb (1935) determined the effects of various anaesthetic and analgesic agents on C.S.F. pressure of cats as recorded by a needle in the cisterna magna. The drugs were administered to cats recovering from ether anaesthesia. These workers found that ether, chloroform, morphine, amylobarbitone and phenobarbitone sodium elevated but bromethol decreased C.S.F. pressure.

Gurdjian and his colleagues (1939) investigated the effects of morphine and of sodium phenobarbitone on the C.S.F. pressure in patients with acute cranial injuries. They reported that morphine caused a persistent rise in C.S.F. pressure but phenobarbitone, in 5 grain (0.32 mg) intramuscular doses, did not influence C.S.F. pressure. In further studies in head injury cases Gurdjian and Webster (1944) found that a mixture of chloral hydrate and sodium bromide caused no rise, and a combination of codeine and pentobarbitone sodium usually caused only a slight rise in C.S.F. pressure. Bedford (1946) studied the C.S.F. pressure changes produced by various drugs in dogs anaesthetized with sodium amylobarbitone. He found that ethanol, methanol, paraldehyde and acetone, administered by inhalation or by injection, had no direct effect on C.S.F. pressure. If the drugs were given in sufficient dosage to cause a fall in blood pressure a parallel fall in C.S.F. pressure occurred.

In 1952 Kepes reported that morphine, given intravenously in various doses, consistently caused an elevation of C.S.F. pressure. She also found that intravenous pethidine almost invariably elevated C.S.F. pressure, the degree of rise depending on the dose. The peak was reached 5–7 minutes after the intravenous injection of pethidine and the pressure had not returned to the original level after 20 minutes.

Keats (1954) has recently studied C.S.F. pressure changes through an intrathecal polyethylene catheter with the patients in the supine position throughout the observation period. He found that 10 mg of morphine injected intravenously caused a maximum rise in C.S.F. pressure of 50 mm H_2O which was usually sustained but occasionally returned to normal within 20 minutes. Ten mg of N-allylnormorphine administered intravenously caused a maximum rise in C.S.F. pressure of 35 mm H_2O. If morphine was administered after N-allylnormorphine the greatest pressure rise was only 15 mm H_2O. N-allylnormorphine administered after morphine resulted in a fall in C.S.F. pressure; the maximum decrease observed was 25 mm H_2O.

The present investigation was designed to determine the effects on C.S.F. pressure of Nisentil HCl* (1, 3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride), an analgesic agent used to supplement N_2O-O_2-thiopentone sodium anaesthesia (Siker, Foldes, Pahk and Swerdlow, 1954), and of levallorphan tartrate† (levo-3-hydroxy-N-allylmorphinan tartrate) which has been shown to antagonize Nisentil-induced respiratory depression (Foldes, Swerdlow and Siker, 1955).

MATERIAL AND METHOD

The observations were carried out on 60 patients, 31 males and 29 females, who were to receive spinal anaesthesia for surgery. The ages of the subjects ranged from 16 to 74 years (average 48.9 years); their weights ranged from 110 to 260 lb. (average 158 lb., i.e. 72 kg). The patients were premedicated with 50 to 100 mg of pentobarbitone sodium given orally $1\frac{1}{2}$ hours pre-operatively, and with a combination of 5 to 10 mg of morphine and 0.2 to 0.4 mg of scopolamine, given subcutaneously one hour before the observation period.

When the patient arrived in the anaesthetic room (which was kept quiet during the test period) an intravenous infusion of 5 per cent dextrose in normal saline was begun. All injections of Nisentil and levallorphan were made into the tubing without the knowledge of the subject in order to exclude any psychological responses. The drip was run at 20 to 30 drops per minute and was only speeded up for a few seconds after each injection. The patient was requested to lie still and to refrain from talking. He was turned on his side, a suitable pillow was placed under his head, and lumbar puncture was performed with a No. 20 spinal needle in the 4th or 5th lumbar interspace. With the spinal needle *in situ*, the patient was permitted to unbend a little and assume a relaxed position. A water manometer was connected to the spinal needle and the C.S.F. pressure was allowed to stabilize for 5 minutes The maximum and minimum levels observed during the last 2 minutes were recorded. The mean of these two figures was taken as the control value. The Nisentil solution used contained 15 mg/ml and the levallorphan solution 1 mg/ml. One-third of 1 mg of Nisentil per kg of body weight was chosen as the standard dose. The dose level of levallorphan was

*For brevity this compound will be referred to hereafter as Nisentil.

†For brevity this compound will be referred to hereafter as levallorphan. These materials were supplied by Hoffmann-La Roche Inc., Nutley, N.J., U.S.A.

1/150 mg/kg (i.e. a 1:50 ratio with Nisentil). The tests were carried out as follows:

(1) Fifteen patients received Nisentil alone. C.S.F. pressure readings were taken at one-minute intervals for at least 10 minutes after the administration of Nisentil.

(2) Fifteen patients were given Nisentil and the C.S.F. pressure recorded at one-minute intervals for 5 minutes. At the end of the fifth minute levallorphan was administered. Pressure readings were continued at one-minute intervals for at least another 5 minutes.

(3) Fifteen patients were first given levallorphan and, after five C.S.F. pressure readings at one-minute intervals, Nisentil was given. The recordings of C.S.F. pressure were continued for a minimum of 5 minutes.

(4) Fifteen patients received a mixture of both drugs and the C.S.F. pressures were recorded at one-minute intervals for at least 10 minutes.

All findings were expressed in per cent changes of control values.

RESULTS

Many of the patients became drowsy or slept lightly following the administration of Nisentil. In addition, it was noted that Nisentil caused wealing along the line of the injected vein in 3 cases and pruritus in one patient. There was a high degree of scatter in the initial C.S.F. pressure readings in the individual patients in each group. The intravenous administration of Nisentil and levallorphan resulted in *marked* changes in C.S.F. pressure. These changes, which are summarized in table I, will be discussed in detail under various headings.

C.S.F. Pressure Changes After Nisentil.

The figures of table I show that Nisentil caused a rapid rise in the C.S.F. pressure which reached a maximum of 69.4 per cent above the mean control level 5 minutes after injection. At the end of 10 minutes the increased C.S.F. pressure had barely started to decline (fig. 1). In the few cases in which measurements were continued for an additional 2–5 minutes there was no marked decrease of the elevated C.S.F. pressure.

TABLE I

C.S.F. pressure changes expressed in per cent of control values

Sequence of drug administration	Time in minutes									
	1	2	3	4	5	6	7	8	9	10
Nisentil alone	10.3 ±2.9(a)	32.8 ±7.6	54.5 ±11.0	62.4 ±12.9	69.4 ±11.9	67.4 ±10.8	64.7 ±9.7	66.1 ±11.2	66.2 ±11.0	58.2 ±9.7
Nisentil followed by levallorphan	6.2 ±2.0	28.6 ±4.6	49.9 ±5.9	61.7 ±6.7	67.4(b) ±6.4	61.2 ±8.2	47.2 ±5.8	35.0* ±4.1	27.7* ±4.2	24.1* ±3.5
Nisentil preceded by levallorphan	−0.6 ±2.1	−3.0 ±3.0	−1.5 ±3.5	−3.1 ±3.5	−2.8(c) ±4.3	0.1* ±3.3	16.3 ±7.2	27.7* ±9.4	41.1 ±11.4	43.1* ±11.2
Nisentil together with levallorphan	8.5 ±2.8	16.6* ±3.8	26.3* ±4.4	41.2 ±7.6	45.0 ±8.4	47.0 ±8.7	47.1 ±8.6	49.5 ±9.2	37.4* ±8.5	41.6 ±9.5

(a) All figures given below the pressure changes are standard errors.
(b) Levallorphan administered.
(c) Nisentil administered.
* Indicates statistical significance.

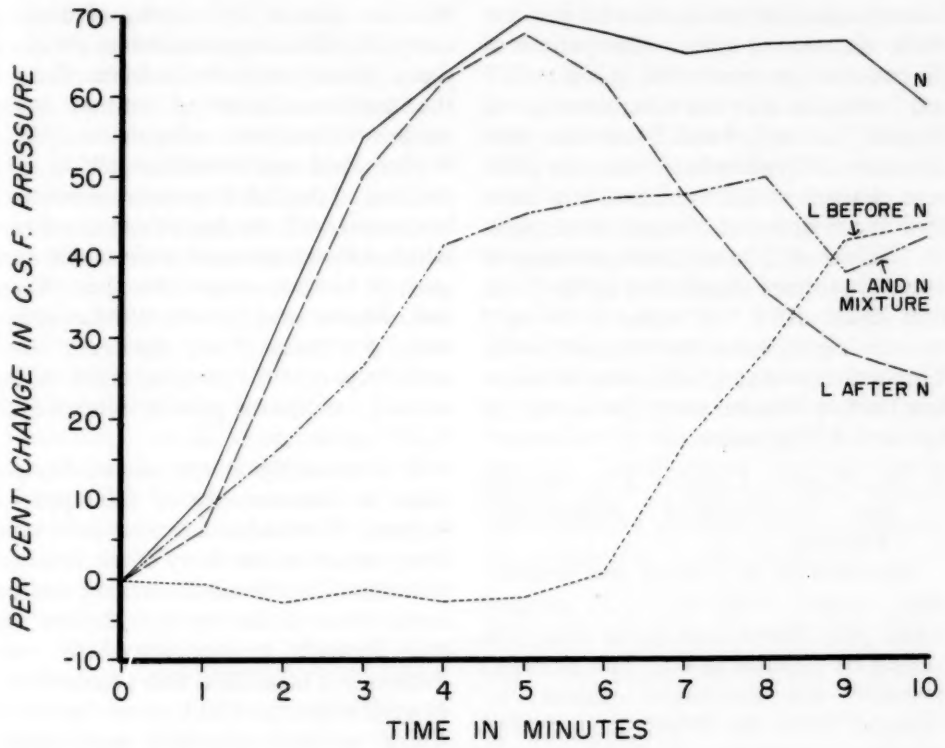

FIG. 1

The spinal fluid pressure curves after Nisentil alone (N); Nisentil followed by levallorphan (L after N); Nisentil and levallorphan administered together (L and N mixture); and Nisentil preceded by levallorphan (L before N).

C.S.F. Pressure Changes After Nisentil Followed by Levallorphan.

When levallorphan was administered 5 minutes after Nisentil it caused a sharp fall in the elevated C.S.F. pressure. Statistical comparison of the mean C.S.F. pressures at 8, 9 and 10 minutes in this group, with the pressures observed after Nisentil alone, shows that levallorphan counteracted significantly the Nisentil-induced elevation of C.S.F. pressure. The corresponding "t" values of 2.6, 3.3 and 3.3 respectively at 8, 9 and 10 minutes are statistically significant (below the 5 per cent level of probability).

C.S.F. Pressure Changes After Nisentil Preceded by Levallorphan.

Levallorphan caused a slight, but not significant fall in C.S.F. pressure. This may have been due to reversal of the effects of premedication on C.S.F. pressure. The administration of Nisentil 5 minutes after levallorphan resulted in a rise of pressure which, at the end of 10 minutes (i.e., at 5 minutes after the

Nisentil administration), was 43.1 per cent above the control value. Comparison of the pressure changes in this group at 1, 3 and 5 minutes after the administration of Nisentil (i.e., at 6, 8 and 10 minutes after injection of levallorphan) with the pressure changes at the corresponding times after the injection of Nisentil alone, gives "t" values of 2.0 and 1.8 respectively at 1 and 3 minutes (significant at the 5 per cent level) and a "t" value of 1.6 at 5 minutes (significant at the 7 per cent level). This indicates that levallorphan administered before Nisentil partly prevented the rise in C.S.F. pressure.

C.S.F. Pressure Changes After Nisentil and Levallorphan Administered Together.

The mixture of Nisentil and levallorphan caused a rise in C.S.F. pressure which was slower and lower than that caused by Nisentil alone. The increased pressure was maintained almost unchanged from the fourth to the tenth minute. Comparison of the pressures in this group of patients at 2, 3 and 9 minutes with the pressures at the corresponding times in the group which was given Nisentil alone, shows that there was a significant difference between the two series. The corresponding "t" values at 2, 3 and 9 minutes respectively were 1.9, 2.4 and 2.1 which are all significantly below the 5 per cent level of probability.

DISCUSSION

It is apparent that Nisentil, in the dosage employed in this study, caused a marked rise in the C.S.F. pressure, which rise was fairly well maintained throughout the observation period. (It should be noted that the dose of 1/3 mg/kg of Nisentil used is considerably greater than the single doses of this narcotic recommended for the supplementation of nitrous oxide-oxygen-thiopentone anaesthesia (Siker, Foldes, Pahk and Swerdlow, 1954). This increase in the C.S.F. pressure is no doubt associated with the respiratory depression which follows administration of the analgesic; it has been shown (Stephen, Woodhall, Martin and Nowill, 1954; Goldensohn, Whitehead, Parry, Spencer, Grover and Draper, 1951) that the depth of pulmonary ventilation greatly influences the C.S.F. pressure.

Unfortunately, it was not usually possible to measure the C.S.F. pressure beyond 10 minutes because this would have caused undue delay of the operating schedule. Circumstances necessitated premedication of the patients before they were brought to the anaesthetic room. Although it is realized that premedication in itself might have had some effect on the C.S.F. pressure this effect was compensated for by the comparative nature of the study. Furthermore, the sedative effects of premedication greatly reduced the patients' apprehension and thus helped to eliminate the effect of psychological factors on C.S.F. pressure.

The results show that levallorphan administered before, after or together with Nisentil, antagonized the rise in C.S.F. pressure observed after Nisentil alone. The fact that the statistical significance of this antagonism was not consistent throughout the observation periods was due primarily to the considerable variation in the C.S.F. pressure response to Nisentil administered alone.

Since the administration of levallorphan

before or together with Nisentil, in a 1 : 50 ratio, decreased the rise of C.S.F. pressure observed after Nisentil and other potent analgesics given alone (Swerdlow, in preparation), the use of such combinations to supplement thiopentone sodium anaesthesia in neurosurgical patients would seem to be indicated. After it had been shown in a large group of surgical patients that levallorphan, in a 1 : 50 ratio, counteracted most of the undesirable respiratory effects of Nisentil, without unduly interfering with analgesia (Foldes, Swerdlow, Lipschitz, Weber and Pirk, in preparation), small doses of a 50 : 1 Nisentil-levallorphan mixture were used to supplement thiopentone sodium anaesthesia for craniotomies. Although measurements of C.S.F. pressure were not made in these patients it was the impression of the surgeons that no undue rise occurred. The 50 : 1 mixture of Nisentil and levallorphan was also used to provide analgesia for pneumoencephalograms. The pertinent findings will be the subject of a subsequent communication (Foldes, Bragdon, Weber and Hershey, in preparation).

SUMMARY AND CONCLUSION

(1) The C.S.F. pressure changes induced by Nisentil HCl alone and by levallorphan tartrate in combination with Nisentil were studied in 60 patients.

(2) Four groups of 15 patients each received respectively: Nisentil HCl; Nisentil HCl followed 5 minutes later by levallorphan tartrate; levallorphan tartrate followed 5 minutes later by Nisentil HCl; and a mixture of the two drugs. In each case C.S.F. pressure readings were taken at one-minute intervals for at least 10 minutes. The dose of Nisentil HCl was 1/3 mg/kg and that of levallorphan tartrate 1/150 mg/kg. Both drugs were administered intravenously.

(3) Nisentil HCl caused a marked rise in the C.S.F. pressure which was well maintained at the end of the observation period. Levallorphan tartrate, given before, after or together with Nisentil HCl, partially prevented or counteracted the elevation of C.S.F. pressure.

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MECHANICAL VENTILATION IN THORACIC SURGERY WITH A NEW PULMOFLATOR

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MECHANICAL artificial respiration during thoracic surgery has been a theoretical ideal in the minds of many engaged in this field ever since the work of Crafoord (1938). Despite the fact that for some years now excellent machines to carry out this function have been on the market, they are still not in universal use. Many feel that the human hand is more informative and controllable than any machine so far invented (Esplen, 1952; Mushin and Rendell-Baker, 1953; Williams, 1954). Such coarse obstruction of the airway as may occur during thoracic surgery by secretions or by the kinking of a bronchus is readily felt, but with experience more delicate observations can be made. The lessened resistance to ventilation from the relief of pulmonary congestion following mitral valvotomy or from the excision of merely a portion of calcified pericardium can be a useful prognostic sign. It may be that here is a possible reason for not using a complicated apparatus to maintain ventilation during the more delicate intrathoracic operations. There is, however, a place for mechanical respiration during anaesthesia so it is necessary to consider the essential requirements of such an apparatus.

Since the combination of thiobarbiturate, nitrous oxide and muscle relaxant is in almost universal use it is unnecessary to cater for the administration of cyclopropane and indeed this is frequently contraindicated by the use of the diathermy. To avoid confusion the term " inflation " will be used to indicate the phase of mechanically produced respiration corresponding to inspiration in the normal cycle. Most mechanical respirators allow a free passive expiration, so this term will be used as for normal respiration.

The basic requirements are therefore:

(1) Length of inflation and expiration must be independently variable over a reasonable range. Inflation must pass immediately to expiration, that is, there must be no pause in which the lung is held inflated at a constant pressure. Expiration must be completely unobstructed.

(2) The pressure built up on inflation must be readily adjustable. There must also be a safety valve which can be set to blow off at a pressure of 30 cm of water or less.

(3) It must be possible to hold inflation temporarily at any pressure up to the maximum to allow for the temporary inflation of the lung. Similarly it must be possible to arrest the cycle readily in the expiratory phase.

(4) It must be possible to change quickly

from hand to mechanical ventilation and *vice versa* and also to accommodate the return of spontaneous respiration.

(5) The apparatus should be as simple as possible and not produce any noise which is not useful in assessing respiration.

Devices for artificial ventilation deliver gases to the lungs to either a preset volume or a preset pressure. The former include all the machines in which a piston is responsible for creating the inflation impulse. As Mushin (1954) has pointed out, a constant defect of this type of apparatus is that in order to vary the pressure to which the lungs are inflated, it is necessary to spill off a portion of the volume of the pressure stroke during which the lungs are held inflated. This is equivalent to lengthening the inflation part of the cycle and by inference from the work of Motley *et al.* (1948), Cournand *et al.* (1947), as reviewed by Watrous *et al.* (1950), the cardiac output will fall. The better known examples of respiration pumps are Pinson's Pulmonary Pump (Pinson and Bryce, 1944), Blease's (1946) Pulmoflator (Mushin and Rendell Baker, 1953), Mørch's (1948) Automatic Machine, James's (1950) Respirator, the Beaver (1953) Respirator, the Radcliffe Respiration Pumps (Russell and Schuster, 1953) and Engström Universal Respirator (Engström, 1954). Some of these have means whereby the stroke volume can be adjusted readily to overcome the objection mentioned above.

Most of the machines in popular use during anaesthesia depend upon the rise in pressure to end the inflation period. The means whereby this is achieved may be mechanical in machines such as the Frenckner Spiropulsator (Mørch, 1948), the 1950 version of the Blease Pulmoflator (Musgrove, 1952), the Williams Pulmoflator (Williams, 1954) and the Aintree Respirator (Esplen, 1952). The cycling is electrically controlled in Mørch's (1952) Respirator (Mushin and Rendell-Baker, 1953), the Newcastle Respirator (Pask, 1953), the Bang Respirator (Bang, 1953) and the Clevedon Respirator (Macrae *et al.*, 1953). Donald's Servo and Puffer Respirators (Donald and Lord, 1953; Donald, 1954) have a photoelectric control, while Beaver and Byford's (1954) Apparatus has an electronic mechanism.

EXPERIENCE WITH THE WILLIAMS RESPIRATOR

As will be seen from the original papers referring to the various respirators mentioned above, they are not all designed for the same purpose. Many of them are not even intended for use during anaesthesia. It was therefore with pleasure that I was able to try out a prototype of the Williams respirator through the courtesy of the British Oxygen Company. This apparatus has been developed and used extensively by the designer as a "third hand" to assist the anaesthetist for varying periods during the course of a major operation. It is not intended that it should be in sole charge of the patient's ventilation for the duration of the operation, and so it seemed to me that such a simple piece of apparatus could be of great help during thoracic anaesthesia without minimizing the value of manual ventilation.

I have used this apparatus intermit-

tently for the last twelve months but am only presenting records of its use in 33 cases. These cases are chosen only because during the anaesthetic I was able to make detailed or useful observations. The patients' ages ranged from 6 to 73 years, 26 of them being over 40 years old. Twenty-seven of the operations were intrathoracic. The periods of continuous ventilation effected by the pump ranged from 4 minutes to 4¼ hours.

The anaesthetic technique was thiopentone-tubocurarine-nitrous oxide-oxygen for induction and maintenance. The majority of the fit adults received a total of 500 mg thiopentone while the highest dose was 600 mg. The two children 3 B.D. and 23 A.M. had rectal thiopentone followed by nitrous oxide-oxygen-tubocurarine. No thiopentone was given to Child 27 T.R. as he was considered too ill. All cases were intubated, usually with an orotracheal tube. Cases 6 C.M., 19 H.L., and 22 J.E.B., had an endobronchial tube in place, while a Karlen's tube was used in Case 29 R.B. In the majority of cases I used a Waters type absorber connected to the catheter mount as is my usual practice for thoracic anaesthesia. Thus in only 2 cases was trichlorethylene used.

A summary of the effect of pump respiration in these 33 cases is given in table I. From column 7 of this table it will be seen that 2 patients showed a definite rise in blood pressure while 12 showed a fall during pump respiration. In 7 cases this fall was moderate or severe and 2 patients became temporarily pulseless.

Cases showing a rise in blood pressure after instituting pump respiration.

Case 2 W.B. This man was a heavily-built retired butcher undergoing a partial gastrectomy for ulcer and also the repair of a L.I.H. The rise in blood pressure here was almost certainly due to underventilation, as it began to fall soon after commencing manual ventilation with an absorber in the circuit. The pressure at which the pulmoflator was set to cycle, 15–17 cm H_2O, was unlikely to give efficient ventilation in such a person with a closed chest.

Case 28 J.M. was a man undergoing partial gastrectomy for ulcer. His blood pressure climbed from 140 mm Hg to 205 mm Hg during pumping despite the use of an absorber. The pulmoflator was set to cycle at 11–15 cm water and after reverting to manual ventilation the blood pressure soon began to fall. Hence underventilation is again the likely reason for the hypertension.

Cases showing a fall in blood pressure after instituting pump respiration.

Case 4 E.L. A rather heavily built woman suffering from a carcinoma of her stomach and having a generalized neurofibromatosis and a haemoglobin of 58 per cent. The pulmoflator was used for three periods at a rate of 14/min with inflation 2½ sec: expiration 2½ sec. The longest period of mechanical ventilation was 40 minutes when her blood pressure fell from 120 mm Hg to 60 mm Hg in this period.

In the light of subsequent experience I feel that the cycling pressure of 21 cm of water was unnecessarily high. Her pulse rate, however, was between 100 and 120/min during most of the operation, and she died 12 hours after operation in congestive heart failure which would seem unrelated to mechanical ventilation.

Case 5 F.W. Operation performed in December in a theatre temperature of 71°F (21.5°C) when the patient's temperature fell to 94°F (34.5°C) before the end of the operation. His pulse rate was mainly between 50 and 60/min throughout the operation except during a period of rapid blood loss. The pulmoflator was used for one period of 50 minutes at a rate of 8-9/min, inflation 3½ sec, expiration 3½ sec, and cycling pressure 12 cm water. During the period of mechanical ventilation the blood pressure fell from 110 mm to 65 mm Hg and rose again to 80 mm within 20 minutes. His condition deteriorated and he died 9 days later with a coliform empyema.

Case 6 C.M. An old-looking man who had been off work for 7 months. Anaesthesia was with a total of 500 mg thiopentone and 41 mg tubocurarine with 60 per cent nitrous oxide and 40 per cent oxygen *via* a left endobronchial tube. Mechanical ventilation was used for two periods of 10 and 7 minutes each. During the first period a rate of 14/min was maintained with a cycling pressure of 24 cm of water. The length of inflation was 2 seconds and expiration 2½ seconds. The blood pressure fell from 140 mm to 75 mm Hg within 13 minutes and had risen again to 135 mm in 3 minutes after reverting to manual ventilation. During the second period a rate of 16/min was maintained with a cycling pressure of 19 cm of H_2O and inflation 2 sec, expiration 2 sec. The blood pressure fell from 135 mm Hg to 75 mm in 5 minutes, while 2 minutes later the man was pulseless. The blood pressure rose to 115 mm Hg spontaneously 5 minutes after the return to manual ventilation, which seemed adequate when the pressure swing was +18 +2 cm H_2O, again suggesting that the cycling pressure was higher than necessary.

TABLE I — Operating — Duration of — Effect on

TABLE I

Case	Sex	Age (years)	Operation	Operating time		Duration of pumping		Effect on circulation	Result
				hr	min	hr	min		
1 D.C.	F	65	Cardio-oesophagectomy for cancer	5	33	5	–	Nil	Died 7 days later
2 W.B.	M	64	Gastrectomy for ulcer, L.I.H.	1	48	–	47	B.P. rise	Normal convalescence
3 B.D.	M	5¾	Excision L.L. lobe and lingula for bronchiectasis	2	17	–	57	Nil	Normal recovery
4 E.L.	F	69	Cardio-oesophagectomy for cancer	(About) 2	45	–	52	B.P. fall	Died 12 hours post-operative. Congestive heart failure.
5 F.W.	M	41	Cardio-oesophagectomy for cancer	4	30	–	50	B.P. fall	Died 9 days later. Heart failure
6 C.M.	M	65	R.L. Lobectomy for cancer	3	20	–	19	B.P. fall	Immediate recovery. Satisfactory. Died 7 weeks later
7 F.B.	M	48	Pneumonectomy for cancer	2	37	1	27	B.P. fall	Satisfactory recovery
8 F.L.	F	64	Oesophago-gastrostomy for cancer	5	20	4	15	Initial fall	Initial recovery. Died suddenly 24 hours later
9 A.D.	M	59	Pneumonectomy for cancer	2	20	–	55	B.P. fall	Normal recovery
10 S.G.A.	M	56	Lobectomy for cancer	3	3	–	23	B.P. fall	Normal recovery
11 T.W.	M	48	Cardio-oesophagectomy for cancer	4	33	1	28	Nil	Prolonged convalescence
12 N.E.	M	43	Excision of pharyngeal pouch	2	34	–	43	Incomplete records Nil obvious	Normal recovery
13 W.G.	M	73	Cardio-oesophagectomy for cancer	4	21	–	6	B.P. fall	Died 4 days later
14 W.N.	M	64	Uncompleted cardio-oesophagectomy for cancer	5	8	–	10	B.P. fall	Died 2 days later
15 A.B.	M	48	Pneumonectomy for cancer	2	20	–	20	Nil	Normal recovery
16 H.H.	M	53	Thoracotomy for cancer	(About) 1	20	–	33	Nil	Satisfactory recovery. Inoperable
17 A.B.	M	44	Pneumonectomy for cancer	3	2	1	3	Nil	Satisfactory recovery
18 F.B.	M	42	Pneumonectomy for cancer	2	47	(about) 1	40	Nil	Satisfactory recovery
19 H.L.	M	46	Pneumonectomy for cancer	3	47	2	8	Nil	Satisfactory. Initial recovery. Died 18 days later
20 D.S.	M	56	Retro-pubic prostatectomy	1	50	–	11	B.P. fall	Satisfactory recovery
21 E.H.	F	51	Thoraco-laparotomy and repair of hiatus hernia	1	33	–	33	Nil	Convalescence slow
22 J.E.B.	M	35	Pneumonectomy for bronchiectasis	2	44	–	30	Nil	Convalescence normal
23 A.M.	F	6	Ligation patent ductus arteriosus	1	43	–	15	Nil	Recovery normal
24 P.P.	F	54	Thoracotomy for removal of mediastinal tumour	1	23	–	55	Nil	Recovery normal
25 W.B.	M	33	Thoracotomy for cancer	1	30	–	57	Slight fall	Recovery satisfactory. Inoperable
26 C.T.	M	26	Partial gastrectomy for ulcer	2	53	2	–	Nil	Recovery normal
27 T.R.	M	6	R.U. Lobectomy for torn bronchus	(About) 1	30	–	55	Records incomplete Nil obvious	Recovery satisfactory
28 J.M.	M	52	Partial gastrectomy for ulcer	2	15	–	55	B.P. rise	Recovery normal
29 R.B.	M	33	Segmental lobectomy for bronchiectasis	2	43	–	4	Nil	Recovery normal
30 M.L.	F	60	Partial gastrectomy for cancer	(About) 1	15	–	38	Records incomplete	Died from extension of growth to bronchus
31 E.B.	F	59	Pneumonectomy for cancer	2	46	–	50	Nil	Recovery satisfactory
32 M.D.	F	61	Thoraco-laparotomy and repair hiatus hernia	2	8	1	5	Nil	Died 10 days later. Pulmonary embolus
33 E.H.	F	65	Cardio-oesophagectomy for cancer	4	25	–	12	B.P. fall	Initial recovery. Died 10 hours later

Case 7 F.B. A well-built schoolmaster with an almost inoperable cancer. Mechanical ventilation was carried out for 1 hour 27 minutes at a rate of 18–20/min with a cycling pressure of 12 cm water. The length of inflation was 1¼–1¼ sec and expiration 1½–2 sec. The blood pressure fell from 115 mm to 80 mm Hg within 5 minutes of instituting mechanical ventilation, but within a further 10 minutes had risen spontaneously to 120 mm Hg at which level it remained. The pulse rate was around 120/min throughout the operation but the fall in blood pressure coincided with a rise to 140/min and it is therefore likely that the period of hypotension was related to the operation itself, and not to the mechanical ventilation.

Case 8 F.L. This patient had, in addition to her disease, an aortic diastolic murmur with a blood pressure of 170/90 mm Hg. The pulmoflator was used continuously for 4½ hours. Though there was an initial fall in blood pressure, similar fluctuations occurred throughout the operation and were not readily explainable, but appeared unrelated to mechanical ventilation.

Case 9 A.D. This man had an uneventful operation and recovery period. Mechanical ventilation was carried out for one period of 55 minutes at 12 and 18/min with a cycling pressure of 11 and 12 cm water. The length of inflation was 2½ seconds and expiration 1 and later 2 seconds. The blood pressure fell gradually from 120 mm Hg to 60 mm Hg in 50 minutes, but this coincided with a rise in pulse rate from 60–90/min and an interruption in blood transfusion, which might well have caused the circulatory deterioration.

Case 10 S.G.A. This case, together with 6 C.M. were the two most dramatic instances of hypotension. The patient was a well-built euphoric man who, two weeks previously, had had a secondary tumour removed from the left frontal region of his brain. He now had a left upper lobectomy for the removal of the primary carcinoma of bronchus. Unfortunately, owing to lack of assistance, records are incomplete. Mechanical respiration at a rate of 12/min was commenced just after the pleura was opened. After 23 minutes the blood pressure had fallen from 110 mm to 40 mm Hg when the radial pulse disappeared and aortic pulsation was seen to be almost absent. The tissues otherwise appeared normal and the surgeon noticed no change. Four minutes after reverting to manual ventilation the radial pulse was only just palpable and 20 mg of methylamphetamine was given intravenously. Two minutes later the blood pressure was 60 mm Hg and the patient's condition ceased to give any anxiety. Three more minutes elapsed and the blood pressure was 115 mm Hg. During manual ventilation a pressure of +4 +12 cm H_2O was giving adequate ventilation and I feel certain that I had set the pulmoflator cycling pressure higher than this. The rest of the operation and the patient's convalescence were completely uneventful.

Case 13 W.G. An old man with a pre-operative blood pressure of 110/80 mm Hg and Hb of 74 per cent. Throughout operation his blood pressure was labile and during a period of 15 minutes when a student was manipulating the rebreathing bag there was a fall from 100 mm to 55 mm Hg. Mechanical ventilation was carried out for 6 minutes at a rate of 16/min and a cycling pressure of 7 cm water. The length of inflation was 2 seconds and of expiration the same. The blood pressure fell from 80 mm to 45 mm Hg during this period and had risen spontaneously to 85 mm Hg 18 minutes afterwards. The pressure used during mechanical ventilation was lower than had been used earlier in the operation when there was no blood pressure change with manual ventilation.

Case 14 W.N. A 64-year-old man who admitted taking 5–15 pints of beer each night. His pre-operative blood pressure was 110/70 mm Hg. Mechanical ventilation was carried out for 10 minutes some 2½ hours after the beginning of the operation. The rate was 10/min at a cycling pressure of about 20 cm of H_2O and inflation and expiration were both 3 seconds in duration. The blood pressure fell from 100 mm to 55 mm Hg in this period and rose again spontaneously, after reverting to manual respiration, to 90 mm Hg within 13 minutes. The pulse rate varied between 70 and 120/min; the higher figures being later in the operation when the patient's condition had deteriorated seriously and the operation was abandoned. Pre-operative E.C.G. showed ventricular and supraventricular extrasystoles while tracings taken during mechanical ventilation showed a normal record.

Case 20 D.S. This patient was an Indian with a blood pressure of 220/140 mm Hg. Mechanical ventilation was commenced after the prostate was enucleated and continued for 13 minutes. In this time the blood pressure fell from 140 mm Hg to 105 mm Hg. After manual ventilation was resumed there was an initial rise in blood pressure to 130 mm Hg followed by a fall to 90 mm and 5 minutes later the patient was pulseless. As the pulse had been slow (50–66/min) throughout and the intravenous injections of 20 mg methyl-amphetamine now restored the blood pressure to 140 mm Hg, I felt that the fall was a reaction to blood loss. It seems likely that this change commenced during the period of pump respiration.

Case 25 W.B. This man had a pre-operative blood pressure of 140/80 mm Hg. Pump respiration was commenced when the pleura was opened and a deliberate attempt was made to produce a fall in blood pressure by the use of high cycling pressures and incorrect ratio of inflation to expiration. The figures were:

Rate	Inflation	Expiration	Pressure
11/min	2 sec	4 sec	8 cm H_2O
14/min	3½ sec	1½ sec	20 cm H_2O
10/min	4 sec	1½ sec	26 cm H_2O
	4½ sec	1½ sec	20 cm H_2O

I did succeed in reducing the blood pressure in the first half-hour from 145 mm Hg to 95 mm Hg but despite the use of the higher pressures could produce no further fall in the second half-hour. The pulse rate was consistently 100/min throughout.

Case 33 E.H. This patient was a very thin woman with a pre-operative blood pressure of 130 mm Hg. Pump respiration was employed for 12 minutes at a rate of 10/min and a cycling pressure of 17 cm of water. Inflation and expiration were equal at 3½ seconds each. During this period the blood pressure fell from 105 mm Hg to 66 mm Hg and rose again

spontaneously to 100 mm within three minutes of reverting to hand ventilation.

DISCUSSION

While I think it cannot be denied that there is a place for mechanical ventilation during anaesthesia, I am equally certain that there is still a place for manual ventilation during all operations. It was very largely in an attempt to decide in my own mind the relative places to be assigned to the two methods that I was glad to have the trial of this apparatus.

As far as the apparatus itself is concerned it is extremely simple to use and observations and adjustments can be made from the usual position in front of the anaesthetic table. The only sound coming from the apparatus is a helpful one. The soft "click" at the end of inflation and expiration is a reassurance that all is well. Any alteration in the preset volume-pressure relationship will affect the cycling. A slowing will result if the gas flows are reduced, as by a cylinder failing or by the development of a small leak in the system; while the apparatus will stop completely if a large leak is present, as when the surgeon opens the bronchus during a pulmonary resection. On the other hand, when the volume of the system is reduced, as by clamping a main bronchus during a pneumonectomy, the rate of cycling suddenly increases. These changes also occur when a leak or an obstruction from any other cause develops in the airway. Irregular cycling can be due to the surgeon handling the lung and altering its volume as well as to the return of spontaneous respiration. This change in cycling will also be manifest by an erratic rise in pressure as shown on the gauge. Thus the pressure-sensitive respirator can do what the intermittent flow gas-oxygen machine has already done in a more limited field, that is to extend the sense of hearing in the clinical conduct of anaesthesia.

In function the Williams Pulmoflator is widely adjustable as the following ranges of figures, actually obtained in use, will show: rate of cycling, 6–22 min; length of inflation, 1–8½ sec; length of expiration, ½–7½ sec.

A superficial perusal of the results in 33 cases where 2 cases showed a rise and 12 cases a fall in blood pressure might give the impression that mechanical ventilation during anaesthesia is a somewhat hazardous procedure.

A more detailed study of these cases will, I think, show that this is not so. Of the 12 cases where there was a fall in blood pressure during mechanical respiration it appears that in only 8 was it related to the use of the pulmoflator. Thus in the first 16 cases in which it was used 7 showed blood pressure changes as a result, while in the next 17 cases only 3 did so. Moreover, the average age of all cases was 48 years, whereas the average age of the cases showing blood pressure changes was 58 years.

It is well known from the work of Werkö (1947) that positive pressure respiration often results in a decrease in cardiac output. This aspect of manually assisted and controlled respiration is extensively reviewed by Watrous *et al.* (1950, 1951) and taken in conjunction with the above results emphasizes some of the recommendations already made (Williams, 1954) for the use of the apparatus. It is essential to estimate the minimal inflation pressure required by watching

the manometer for a few moments during manual ventilation, and then setting the pulmoflator to work at this figure. Musgrove (1952) also recommends the individual estimation of inflation pressures.

In the same way the relationship between the lengths of inflation and expiration is important. A normal respiratory cycle consists of three phases: inspiration, expiration, pause. In artificial mechanical ventilation the latter two phases merge into one as far as the machine is concerned. Thus the expiratory phase must be long enough to include a full exhalation and a pause. I find I cannot be certain of this unless I use a stop-watch to time the two phases accurately.

Since the use of too high an inflation pressure or too short a period of exhalation will result in a reduction of cardiac output it is also essential to keep a record of frequent blood pressure and pulse readings and preferably not to bring the pulmoflator into use until they have reached a steady level.

I hope the analysis of these results will point to a moral lesson as well as to a factual one. Every complicated piece of machinery has its price which may even equal the labour it saves or the pleasure it gives. Just as discrimination in the use of films and radio has given them an essential and beneficial place in our lives, so we need wisdom and experience if mechanical respirators are to improve on the work of man's hands.

SUMMARY

(1) The Williams Pulmoflator has proved very useful as a "third hand" in all forms of surgery including the most difficult intrathoracic operations. Its usefulness depends very largely on its simplicity and reliability.

(2) Circulatory disturbances were seen. They occurred early in the series in the older and more frail patients. They were always corrected and largely prevented in later cases as a result of increasing experience and attention to detail.

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ACUTE SUB-GLOTTIC OEDEMA OF THE LARYNX AS A SEQUEL TO ENDOTRACHEAL ANAESTHESIA

BY

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OEDEMA of the larynx has long been recognized as a complication of endotracheal anaesthesia. It appears, however, that the majority of cases which have been described have shown oedema of the vocal cords or of the epiglottis. The peculiar liability of small children to oedema of the infra-glottic tissues has not, in our opinion, received sufficient attention and we believe, therefore, that the following two cases may be of interest:

Case I. B.L., a male child aged 5 years, was admitted to a Chest Unit suffering from bronchiectasis of the lower lobe of the right lung. The operation of lobectomy was accordingly performed on 18.9.46.

Premedication was with atropine sulphate, 1/100 grain (0.65 mg). Anaesthesia was induced with intravenous thiopentone followed by nitrous oxide, oxygen and ether. This presented no especial difficulty and after about ten minutes laryngoscopy was performed.

Endotracheal intubation was attempted with a No. 4 Magill's tube (oral). This passed through the rima glottidis with ease but was held up in the cavity of the larynx. A No. 3 Magill's tube (with cuff) was then tried without success; finally a No. 3 (nasal) was passed with some difficulty.

Anaesthesia was maintained with nitrous oxide, oxygen and ether, using the Waters method of carbon dioxide absorption. The operation was uneventful and was completed in about fifty minutes. Bronchoscopy was then performed by the surgeon with a Negus bronchoscope (9 mm external diameter) with some difficulty.

The events following the operation may be summarized as follows:

+ *2 hours*: "Marked laryngeal stridor and hoarseness. Patient conscious, both sides of chest moving with obvious use of accessory muscles of respiration, marked tracheal tug."

Laryngoscopy: "Cords reddened but no oedema, marked tracheitis." A soft rubber catheter was passed into the trachea and a quantity of thick mucus was aspirated.

+ *6 hours*: "Slight improvement, still marked stridor and hoarseness but colour good and pulse of good volume."

+ *18 hours*: "Intense stridor, colour good (with continuous administration of oxygen)."

+ *24 hours*: "On laryngoscopy: Epiglottis and vocal cords reddened. Mucous membrane of upper trachea thickened and shaggy."

+ *30 hours*: "Tracheotomy was performed under general anaesthesia (cyclopropane and oxygen). Prior to this bronchoscopy was attempted but there was such intense oedema of the sub-glottic tissues that the bronchoscope could not be passed."

The condition of the patient showed marked improvement but death occurred suddenly 38 hours after the original operation. The following changes were recorded at post-mortem examination:

"Pharynx: Normal.

"Larynx: There is rather marked oedema of the vocal cords with obliteration of the right lateral sinus and marked reduction of the left.

"Trachea: For about three-quarters of an inch immediately below the vocal cords there is a white sloughing ring encircling the airway and somewhat obstructing it. The slough peels off with difficulty. There is no sign of acute inflammatory change in the larynx or trachea. The tracheotomy wound is healthy but the trachea below it is obstructed by a large quantity of tenacious mucus which extends down into both lungs but especially into the right.

"The left pleural space contains a small quantity of clear, straw-coloured fluid. The right pleural space contains a small quantity of blood. Neither lung shows any sub-pleural haemorrhage.

"Left Lung: Apart from slight congestion is normal.

"Right Lung: The lower lobe has been removed. The remaining lung has expanded but there has been a fair amount of patchy haemorrhage into its substance and the bronchioles contain the same mucus as is found in the trachea.

"Heart and Aorta: Normal."

Case II. M.N., a male child aged 3 years, was admitted to the Royal Devon and Exeter Hospital on 8.3.54, and on 9.3.54 the operation of Schwartze Mastoidectomy was performed. Routine examination of the respiratory and cardiovascular systems before anaesthesia had revealed no abnormality. Premedication was by hypodermic injection of atropine sulphate, 1/100 grain (0.65 mg) and Nepenthe m4. Anaesthesia was induced with ethyl chloride followed by ethyl

ether on a mask and, following this, laryngoscopy was carried out, and the glottis exposed without difficulty. An attempt was made to introduce a No. 2 Magill's endotracheal tube. This appeared to be the correct size and passed between the vocal cords without difficulty but could not be advanced into the trachea. A further attempt was then made, using a No. 1 tube, and this passed easily. Anaesthesia was continued with oxygen and ether, using Ayre's method, and the operation (which lasted about 45 minutes) proceeded without further incident. The endotracheal tube was then removed. A Guedel's airway was introduced and the child returned to the ward. There was at this stage no evidence of respiratory obstruction. His breathing was quiet and regular and there was no cyanosis.

Subsequent events may be summarized thus:

+ *3 hours*: "Slight stridor apparent."

+ *7 hours*: "Stridor increased. There is some indrawing of the lower ribs and contraction of the accessory muscles of respiration."

+ *7½ hours*: "Very marked contraction of accessory muscles of respiration. The patient is cyanosed for the first time."

At this stage a diagnosis of respiratory obstruction due, probably, to oedema of the larynx was made and the patient was transferred to the operating theatre.

+ *8½ hours*: Anaesthesia was induced with cyclopropane, oxygen and ether. This presented no particular difficulty and the slight cyanosis disappeared. Laryngoscopy was performed. It was observed that the true and false vocal cords appeared normal. There was, however, oedema of the cavity of the larynx and its lumen was considerably reduced. A soft Magill's endotracheal tube, No. 0, was then introduced without great difficulty, and anaesthesia maintained through it. Tracheotomy was then performed.

Following this the child made a satisfactory recovery complicated only by slight surgical emphysema of the neck. The tracheotomy scar was healed on 23.3.54, and anaesthesia was carried out on 6.4.54 for the operation of myringotomy on the other ear, without any difficulty.

DISCUSSION

In both these cases severe respiratory obstruction developed within a few hours of the passage of an endotracheal tube (followed by bronchoscopy in the first of the cases). Tracheal intubation was, in both instances, difficult, since although the tubes passed through the rima glottidis with ease they were held up within the cavity of the larynx. There is no doubt that, in the first case, the first attempt was made with a tube which was too large and it may be said, in extenuation, that this child had a considerable amount of sputum so that repeated aspiration was required. This, it was thought, could be performed with greater facility and safety through a tube of the greatest possible internal diameter. Nevertheless, the same difficulty was experienced with smaller tubes and, in our second case, the first tube used was of a reasonable size.

In neither case were definite changes observed on laryngoscopy, although, as a result of experience gained in the first case, one of us (K.J.P.) considered that the appearance of the larynx in the second was very suggestive of sub-glottic oedema.

Both cases were relieved by tracheotomy and it is probable that the first patient would not have died had this been performed earlier.

Similar cases have been reported by Baron and Kohlmoos (1951), and Eckenhoff (1951). The first and fourth cases described by the former authors and the latter's second case, conform very closely to the clinical pattern of ours. There is marked similarity also between the post-mortem findings in the first case of Baron and Kohlmoos, the second case of Eckenhoff, and our first case.

We are convinced that both our cases developed oedema within the cavity of the larynx following arrest of an endotracheal tube at the level of the cricoid cartilage. The peculiar features of the infant larynx were noted by Holinger and Johnston (1950) and the anatomical differences between the child and the adult in this respect are admirably reviewed by Eckenhoff (1951). The relevant facts may be summarized as follows:

(1) The smallest internal diameter of the infant larynx is commonly at the level of the cricoid cartilage.

(2) At the cricoid arch the cavity of the larynx is surrounded by a rigid cartilaginous ring.

(3) The mucous membrane of the larynx is closely adherent to the true vocal cords. Elsewhere it is separated from the underlying structures by a variable amount of loose connective tissue.

SUMMARY

(1) Two cases are reported in which sub-glottic oedema of the larynx occurred following the passage of endotracheal tubes.

(2) Children are, in particular, liable to develop this complication since, in childhood, the smallest internal diameter of the larynx may be in the region of the cricoid cartilage.

(3) The possibility that this complication has occurred should be considered whenever upper respiratory obstruction develops following the passage of an endotracheal tube or bronchoscope.

(4) It should be recognized that tracheotomy will almost certainly be necessary in these cases, and that this should be carried out even if the vocal cords appear normal on laryngoscopy.

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FACULTY NEWS

SCIENTIFIC MEETING

The Faculty is holding a further Scientific Meeting on Saturday, July 9, 1955, and this time the symposium will be on the Central Nervous System. Those who have consented to speak are:

The Rt. Hon. Lord Adrian, who will speak on the Physiology of the subject.

Dr. W. Grey Walter, who will speak on "Electro-encephalography in the Study of Brain Disease".

Dr. W. Blackwood, who will speak on "The Pathogenesis of ischaemic and haemorrhagic lesions in the brainstem secondary to raised intracranial pressure".

Dr. B. D. Wyke, who will speak on "Neurophysiological aspects of electrographic monitoring of anaesthesia".

Brit. J. Anaesth. (1955), **27**, 260.

A NEW ENDOTRACHEAL CATHETER FIXATION

BY

RUDOLF FREY

Heidelberg

IN the Anaesthesia Department of the Heidelberg Surgical Clinic we developed a special device of solid rubber (see fig. 1) for fixation of endotracheal catheters (available by W. Walb, Heidelberg, Bergheimerstrasse). Figure 1A shows the device with the catheter in position and the soft rubber band which encircles the head.

Figure 1B shows the solid rubber plug which prevents occlusion of the catheter by the teeth should position of the head bring the jaws together. The area through which the catheter passes is of relatively thin rubber in which there is a cruciform slit enabling catheters of all sizes to be passed, yet firmly held.

In the last two years this fixation was very helpful for us in more than 2,000 intubations, especially in face down and lateral positions.

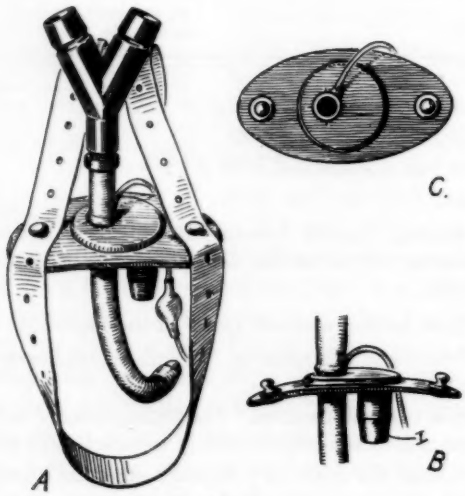

FIG. 1

Brit. J. Anaesth. (1955), **27**, 261.

A TRANSISTOR PULSE COUNTER

BY

L. MOLYNEUX AND E. A. PASK

Department of Anaesthetics,
Medical School, King's College, University of Durham

TRANSISTORS can be used to construct a cardiotachometer with characteristics more favourable than those hitherto available. The photograph (fig. 1) and circuit diagrams (figs. 2 and 3) of an instrument which we now have in use is shown. The advantages gained from the use of transistors seem to be as follows:

(1) Compact dimensions. Our instrument is 10″ high, 7¼″ wide and 5″ deep.

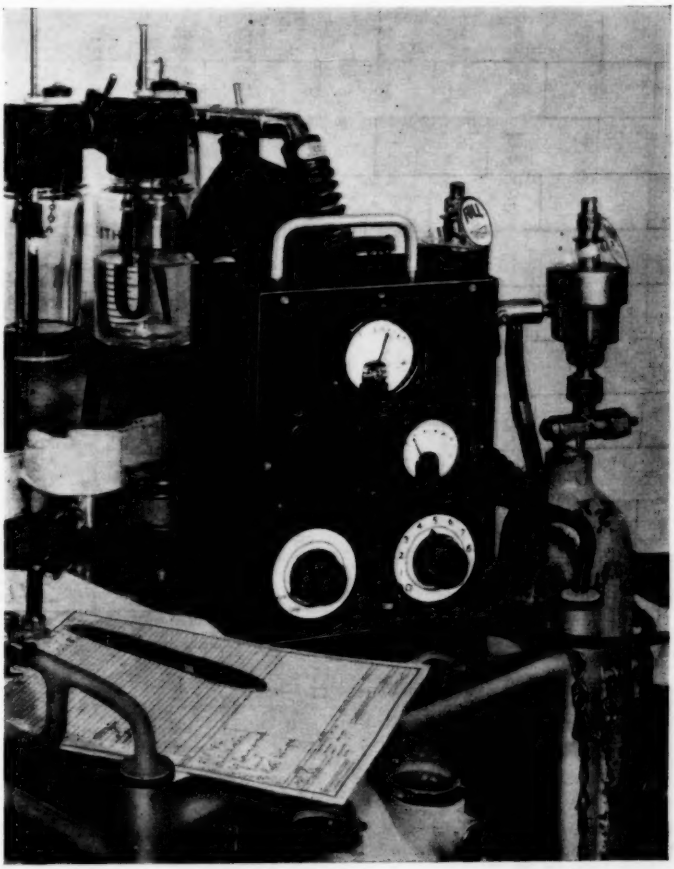

FIG. 1

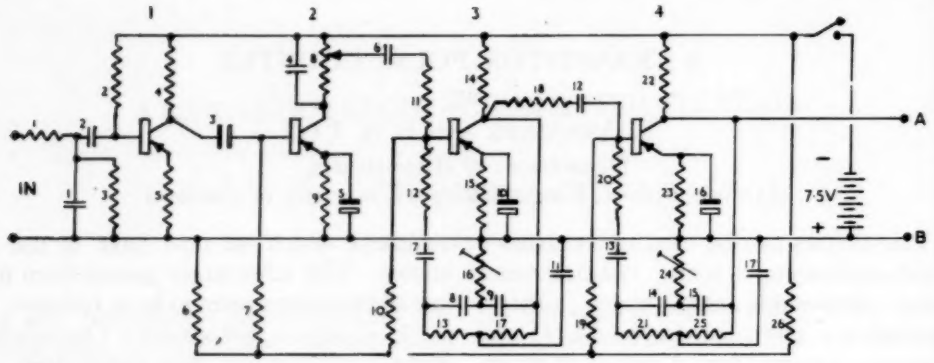

FIG. 2

Resistances in kilohms

1.	1.0	5.	2.7	9.	12	13.	40	17.	40	21.	33	25.	33
2.	390	6.	1.5	10.	82	14.	27	18.	27	22.	27	26.	5.6
3.	820	7.	82	11.	27	15.	12	19.	82	23.	12		
4.	2.7	8.	20	12.	20	16.	20	20.	20	24.	20		

Capacities in microfarads

1.	0.1	4.	0.25	7.	0.5	10.	100	13.	0.5	16.	100
2.	0.25	5.	100	8.	0.5	11.	0.5	14.	0.5	17.	0.5
3.	8.0	6.	0.5	9.	0.5	12.	0.5	15.	0.5		

Transistors

1, 2, 3 and 4 are Mullard Type OC71

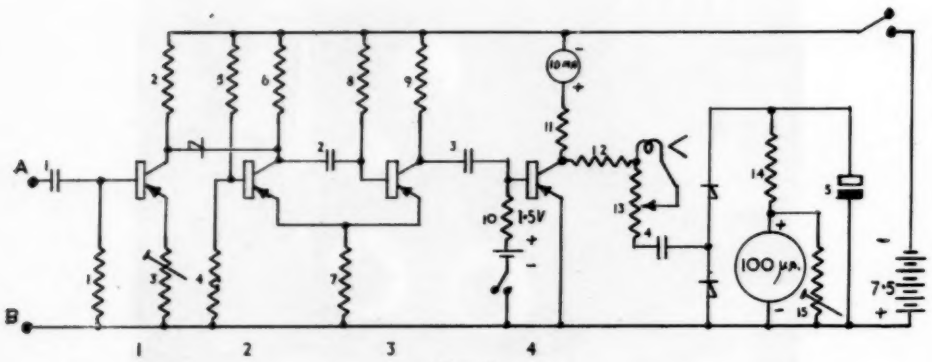

FIG. 3

Resistances in kilohms

1.	100	4.	0.11	7.	0.32	10.	1.0	13.	0.25
2.	22	5.	5.6	8.	470	11.	1.0	14.	2.7
3.	20	6.	15	9.	6.8	12.	0.22	15.	1.0

Capacities in microfarads

1.	0.5	2.	1.0	3.	0.1	4.	6.0	5.	2000

Transistors

1, 2 and 3 are Mullard Type OC71.
4 is Mullard Type OC51

Diodes

All Diodes are Mullard Type OA73

(2) Light weight. Our instrument weighs $8\frac{1}{4}$ lb.

(3) Very economical. Battery operation (total consumption 48 milliwatts). The expected life of internal batteries is in excess of 50 hours.

(4) Because the battery voltage is low, the instrument presents no explosive hazard.

(5) No leads are needed other than those from the instrument to the patient.

The large upper dial continuously displays the pulse rate. The needle of the smaller dial flicks each time the heart beats, so that irregularities are immediately evident. The small loudspeaker, lower left, makes a tiny click every time the heart beats. The amplitude of this click can be controlled.

Connexion to the patient is made either by conventional ECG leads or by sterile needles inserted in the skin of the chest.

ST. JOSEPH HOSPITAL, HEERLEN, LIMBURG, HOLLAND

ANAESTHETIST WANTED, well qualified and trained, who would replace the Hospital Anaesthetist during his three weeks holiday from August 1 till August 21, 1955.

Write all particulars, including references, to Medical Director, H. H. Lindeboom, St. Joseph Hospital, Heerlen, Limburg, Holland.

ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.
Licentiate of the Royal College of Physicians

(*Continued from page* 195)

In certain cases of the medicinal application of chloroform, and also in obstetric cases, where the pains are not severe, it is unnecessary to render the patient unconscious, but for surgical operations this is nearly always requisite. No force should ever be employed so long as the patient is conscious, unless it be to children or lunatics; but some patients become excited as soon as they are unconscious, and attempt to leave the couch, or push away the chloroform; under such circumstances, if they cannot be calmed by what is said to them, they should be held, and the vapour should be steadily and gently continued, for a minute of two, till a state of quietude is produced. By far the greater number of patients remain quiet as they become unconscious, but there is no difficulty in ascertaining whether a patient is unconscious or not. If the eyelids remain open, the countenance shows whether the patient is conscious or not; and, if they are closed, it is only necessary to touch them gently, to ascertain this circumstance. If he is still conscious, he will look at his medical man, and probably speak, or, at all events, show intelligence in his countenance.

Signs of Insensibility. The absence of consciousness, and a state of quietude, are both requisite before the commencement of a surgical operation, and they go a good way towards the preparation of a patient for it, for these symptoms may be present and the patient not be ready for an operation. The surgeon wishes to know whether he will lie still under the knife, or whether he will make a resistance and outcry which he would probably not make in his waking state. Some surgeons have recommended that the patient should be pricked with the point of a knife or some other instrument. This is not a good or satisfactory plan, however, for a person will often show no sign of feeling a slight prick, when a severe incision would rouse him to resistance. A more elegant and successful plan is to raise the eyelid gently, by placing one finger just below the eyebrow, and then to touch its ciliary border very lightly with another finger. This should not be done roughly nor too frequently, for fear of exhausting the sensibility when it is slight. Just after unconsciousness is induced, the eyelids are often closed very strongly when their margins are touched, especially in females, and there seems to be a positive hyperæs-

thesia; this, however, is only apparent, and arises from the control of the will being removed, whilst sensibility remains. By continuing the chloroform, the sensibility of the edges of the eyelids diminishes until, at last, they may be touched without causing winking. Under these circumstances, the most severe operation may, in almost every case, be commenced without sign of pain. I have employed this test of the sensibility or insensibility of the patient ever since chloroform has been in use, and also in the employment of ether in 1847, and I am satisfied that it affords more reliable information on this point than any other single symptom. It even indicates the amount of sensibility where a little remains; when, for instance, touching the margin of the eyelids causes very slight and languid winking, the patient will commonly flinch a little if the knife is used, but only in a manner that can be easily restrained, and will not interfere with the majority of operations. The cases, in which the indication afforded by the eyelids is not always to be depended on, are those of hysterical patients, in whom there is sometimes no winking on touching the eyelids, even when unconsciousness is scarcely induced. In such cases, one must judge by the other symptoms, and also by the length of time the patient has inhaled, the strength of the vapour, and depth and activity of the breathing. Indeed, these conditions should be observed and taken into account in every case; and all the symptoms exhibited by the patient should be watched, such as the expression of the face, the state of the breathing, and the condition of the limbs with regard to their tension or relaxation. The last is indeed sometimes relied on as the chief or sole sign whether the operation may be commenced, but it is of itself very insufficient, and even fallacious. The patient may allow his limbs to lie relaxed when he is scarcely unconscious, and not at all insensible, merely because he is not exerting his will upon them; if the arm is lifted, it may fall listlessly down again, at a time when the knife of the surgeon would rouse the patient to active resistance. Indeed, the limbs, which have been lying relaxed, may become tense as the effect of the chloroform increases, and may remain so during a short operation, in which there is no sign of pain.

Although the pulse of itself gives no indication as to how far a patient is under the influence of chloroform, it is proper to pay attention to it, not only during the first administration of the chloroform, but also throughout the operation, especially if it be attended with much bleeding. The pulse sometimes becomes intermittent or irregular during the administration of chloroform, more especially in elderly persons. This more commonly happens in the first exhibition of it, than when it is repeated during the course of an operation. I have not seen any harm from either of these conditions, but it is well to intermit the chloroform for ten or fifteen seconds, and let the patient have a few inspirations without it, if the pulse is not in a satisfactory condition. If the precaution be taken to ensure that the air the patient breathes shall never contain more than five per cent. of vapour, the pulse can never be seriously affected by the direct action of the chloroform, and the state of the breathing affords the best warning against continuing the inhalation too long at a time.

The breathing is fortunately also a sign that cannot be overlooked. It is by the breath that the chloroform enters, and it is extremely improbable that any one would go on giving the vapour after the breathing became stertorous and laboured.

The patient sometimes holds his breath after he is unconscious, and before he is insensible; this occurs under two conditions: first, after deep and rapid breathing, during which the patient seems to absorb more oxygen than is immediately required, under the circumstances; and in this condition I have known him hold his breath for a whole minute, whilst the pulse was unaffected. The other condition in which the breathing is suspended, is when there is rigidity in the third degree of narcotism, and the respiratory muscles seem to partake of the general rigidity; the holding of the breath in these cases seldom continues so long as under the former circumstances. I do not consider that there is any danger from either of these kinds of suspension of breathing. I believe it always returns as soon as there is a want of oxygen in the system. Of course the inhaler need not be applied to the face when the patient is not breathing, and he may as well have an inspiration or two without chloroform when the breathing is renewed. It is seldom requisite to carry the effects of chloroform so far that the breathing becomes stertorous, and whenever stertor is observed, the inhalation should be suspended; under these circumstances, the patient is always insensible. In some cases, in which a little more chloroform has been inhaled than is necessary, the patient breathes for half a minute or so by the diaphragm only, and breathes in fact hardly at all. The abdomen rises and falls freely, but, from the muscles of the chest not fixing the ribs, hardly any air enters the lungs, and the face becomes rather livid; meanwhile the pulse goes on very well, and at last the patient draws a deep, sonorous inspiration, the face resumes its proper colour, and all is right again. I have not heard of any accident from chloroform commencing in this manner. This state of breathing, when it does occur, usually takes place a few seconds after the inhalation has been left off, and arises from the accumulation of the effects of the chloroform, owing to the absorption into the system of the vapour which was contained in the lungs at the time when the inhalation was discontinued.* This accumulation or increase of the effects of chloroform lasts for about twenty seconds; it is not dangerous unless the vapour is inhaled of too great strength, but it should be borne in mind in all cases. It may be prevented altogether, by reducing the strength of the vapour, just as the patient is getting insensible, or by giving it with intermissions of a few seconds, at this time.

* The increase of effects of chloroform after the inhalation is discontinued, was pointed out by Prof. Sédillot of Strasbourg and myself almost simultaneously. I explained the circumstance in a paper read to the Westminster Medical Society, on January 8th, 1848, and M. Sédillot announced it to the Academy of Sciences of Paris, on January 10th. My remarks were published in the *Medical Gazette* of January 14th, and those of M. Sédillot in the *Gazette Médicale* of January 15th.

(To be continued)

BOOK REVIEW

Nerve Blocks: A Manual of Regional Anaesthesia for Practitioners of Medicine. By John Adriani, M.D. Published by Charles C. Thomas, Springfield, Illinois, U.S.A. Price £2 7*s.* 6*d.*

Dr. Adriani tells us in the preface that "At the suggestion and recommendation of students and friends" he has taken section 5 of his book *Techniques and Procedures of Anaesthesia* on Regional Anaesthesia, revised and enlarged it, and made this separate book of it. This is all to the good. Some of the immense volumes we have seen recently owe their size and cost largely to the inclusion of details of regional blocks. The original section 5 spread over 124 pages; this occupies 250. The increase in size has been distributed in proportion to the extent of the original text, thus for instance the chapter on Spinal Anaesthesia is just about twice as long as in the section 5 of his former book and the illustrations twice as numerous.

The text and illustrations of the field blocks scarcely call for comment, but spinal anaesthesia, being a more controversial subject, lends itself thereto. Dr. Adriani's account is a very fair one. It would nevertheless be easy to find authorities who would differ from him on various points. It would be better under the heading "contra-indications" to divide them into two sections: (*a*) Absolute, such as local sepsis, disease of the nervous system, etc., and (*b*) Doubtful. For example, Dr. Adriani includes under the heading "contra-indications" myocardial disease, hypotension, hypertension, upper abdominal surgery, the aged, and children. Everyone of these "contra-indications" has been considered by experts as a specially suitable indication for spinal anaesthesia. Thus it has been argued that a weak heart has a better chance of dealing with a low than a high blood pressure; also relaxation of the blood vessels gives the heart normally subjected to severe peripheral resistance, a timely rest. There is no region in the body where the surgeon is so dependent on adequate muscular relaxation as the upper abdomen and nothing provides it better than spinal anaesthesia. Parsons and Gray decided that children liable to shock from bone operations were better protected by spinal than by any other type of anaesthesia. It is true that was as long ago as 1912 and it is possible that some modern methods might be as good or better. This remains to be proved. In so far as shock has a neurogenic factor it is difficult to see how any general anaesthetic can take the place of a type of anaesthesia which blocks nerve impulses. In his book on *Techniques and Procedures*, on page 215, he says "It [spinal] is frequently followed by postoperative neurological complications." In the present volume the word "occasionally" has replaced the word "frequently"; this is better and more in accordance with the facts. It is perhaps too much to hope that in the next edition he will be able to replace the word "occasionally" by the word "never". The record of Sebrechts, Babcock and others, and the latest report from Dripps and Vandam who record a follow-up of more than 10,000 cases of spinal anaesthesia without any major neurological complication, brings nearer such a possibility, if only anaesthetists will take the trouble to learn their job and exercise that meticulous care which is essential.

Neither "ampoule", "autoclaving", "sterilization" nor "storing" are mentioned in the index but on page 194 the following advice is given: "Use sealed sterile individual ampules of all drugs and solutions for intrathecal injection. Submerge sealed ampules in alcohol or other suitable cold sterilizing agent. Color sterilizing solutions with suitable dye, such as methylene blue." In spite of all that has been said on this subject ampoules have been kept in spirit, transferred to the anaesthetic table and used without causing any neurological complications. This practice was in operation for over twenty years and it seems to me quite sound. The doubts that have been cast on this practice in recent years rest on flimsy evidence and have only been accepted with great reluctance *faute de mieux*. The book will serve its purpose. It is clearly illustrated, sufficiently dogmatic and beautifully printed on good paper.

E. Falkner Hill

CORRESPONDENCE

DOES LAUDEXIUM CURARIZE?

Sir,—In a recent paper in your journal, Dr. Hunter (1955) claims that neostigmine fails to antagonize satisfactorily respiratory depression in the cat or mouse due to laudexium (Laudolissin), although it antagonizes that due to d-tubocurarine or gallamine triethiodide. In a previous paper (Hunter, 1954), he states that, in the mouse, "fibrillation, fasciculation and vigorous tonic contractions of the limb muscles . . . are produced by laudexium . . . while after d-tubocurarine and gallamine triethiodide, the syndrome of exitus usually consists of head drop and respiratory paralysis with virtually no spontaneous muscular activity."

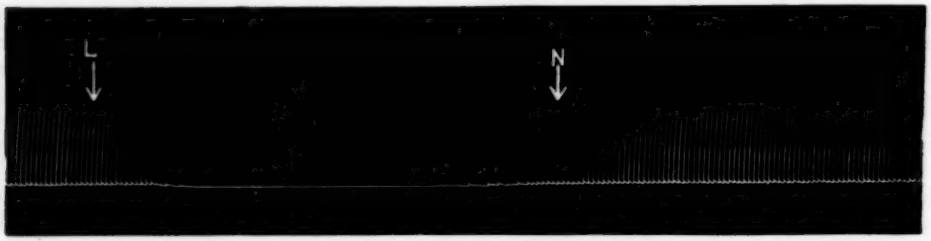

FIG. 1

Cat, chloralose. Twitch of *tibialis anticus*, in response to 1 stimulus of its motor nerve per 10 sec, recorded by isometric myograph. At L, 150 μg laudexium methylsulphate and, at N, 100 μg neostigmine methylsulphate per kg intravenously.

The implication is that laudexium is not a true curarizing agent. We have therefore performed some further animal experiments which we believe have a bearing on this suggestion.

To a cat anaesthetized with chloralose and prepared for recording the *tibialis* twitch, we administered intravenously 150 μg laudexium methylsulphate per kg, which produced full paralysis. This was completely reversed by a single dose of 100 μg neostigmine per kg, as will be seen from figure 1. Dr. Hunter's failure to obtain antagonism of respiratory depression due to a smaller dose of laudexium (100 μg) in cats anaesthetized with pentobarbitone may perhaps be explained by the fact that neostigmine does not antagonize respiratory depression due to barbiturates.

We next compared the power of neostigmine to protect mice against lethal doses of laudexium, d-tubocurarine and gallamine. With each drug, a group of 20 mice received a dose that was expected to kill nearly all animals. A second group received the same dose mixed with neostigmine. All deaths occurred shortly after treatment and these are expressed in the table. It will be seen that neostigmine appears to antagonize d-tubocurarine least well of the three curarizing agents used. The degree of antagonism of d-tubocurarine is nevertheless highly significant. Gallamine is significantly better antagonized than d-tubocurarine. Laudexium is not significantly worse antagonized than gallamine nor better than d-tubocurarine.

In a further 62 mice we investigated the claim that laudexium produces "convulsions" in mice while d-tubocurarine does not. We gave 33 mice d-tubocurarine and 29 laudexium intravenously in doses of corresponding potency ranging from the ineffective to the lethal. After treatment, all mice were carefully observed, usually by one of us who did not know which drug the other had given. It proved impossible to distinguish d-tubocurarine from laudexium by their effects on mice. Curarizing doses of both drugs produced "convulsive"

TABLE

Antagonism by neostigmine methylsulphate of lethal doses of curarizing agents in mice

Curarizing agent		i.v. dose neostigmine		
Name	i.v. dose in mg per kg	in mg per kg	Proportion of mice dying	Proportion of mice saved
d-Tubocurarine chloride	0.4	0	19/20*	
	0.4	0.2	8/20*	11/19§†
Laudexium methylsulphate	0.7	0	18/20	
	0.7	0.2	4/20	14/18†‡
Gallamine triethiodide	6.0	0	19/20	
	6.0	0.2	0/20	19/19§‡

* $\chi^2 = 11.40$, $P = <0.001$
† $\chi^2 = 0.89$, $P = <0.5>0.3$
§ $\chi^2 = 7.76$, $P = <0.01>0.001$
‡ $\chi^2 = 2.69$, $P = <0.2>0.1$

movements, perhaps through partial asphyxia. After lethal doses of either drug, twitching of the skin was sometimes seen just before death. The behaviour of mice given effective doses of d-tubocurarine bore extraordinarily little resemblance to the picture of "virtually no spontaneous activity" presented by Dr. Hunter. Similar "convulsive" effects were also noticed when doses of gallamine were given.

Our present experiments are entirely consistent with experiments we have already published (Collier and Macauley, 1952, 1954), namely that laudexium, like d-tubocurarine, produces flaccid paralysis in the chick, synergizes with ether, fails to stimulate the frog's *rectus abdominis* and potently antagonizes the action of acetylcholine on this muscle. Dr. Hunter does not refer to these experiments and he also omits to draw the obvious conclusion from some of his own findings, for example, that laudexium summates with gallamine and antagonizes RO 3-0386.

We do not dispute Dr. Hunter's thesis that "Instead of describing drugs of this type (myoneural blocking agents) as belonging to two hard and fast groups they should be regarded as substances possessing essentially the same properties but those in varying degree". In fact about 18 months before Dr. Hunter advanced this thesis, one of us (Collier, 1953) discussed this point of view favourably at considerable length. Before that Bovet (1951) had already put this idea forward. We do not know whether gallamine is more curarizing than curare; but we stand quite firm on our original ground, laudexium is similar in mode of action to d-tubocurarine.

H. O. J. COLLIER
BARBARA M. MACAULEY
Research Division,
Allen and Hanburys Ltd., Ware, Herts.

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—— Macauley, B. M. (1952). *Brit. J. Pharmacol.*, **7**, 398.
—— —— (1954). *Brit. J. Anaesth.*, **26**, 237.
Hunter, A. R. (1954). *Brit. J. Anaesth.*, **26**, 399.
—— (1955). *Brit. J. Anaesth.*, **27**, 73.

Sir,—The above letter of Doctors Collier and Macauley serves once again to emphasize the point which I made in my paper to which they refer, that relatively minor differences in technique can profoundly influence the results of experimental studies with relaxant drugs. For example, I found that 400 μg per kg of laudexium methylsulphate was an LD 95 for my mice while they required nearly twice this amount, 700 μg per kg to produce a comparable result. In this instance I should think rates of injection will probably account for this quantitative difference, and probably also for the comparative absence of hyperkinetic phenomena in their animals.

Dr. Collier cannot have it both ways. I would heartily agree with him, if he classifies myoneural blocking agents into true and pseudocurares, that laudexium falls into the former category. If, however, he classifies his relaxants as I suggested in

my paper in your November issue, there can be no doubt that laudexium with its slighter ganglion blocking activity, its smaller tendency to release histamine, and its uncertain reversal by neostigmine in the human subject at least, cannot be regarded as having actions identical with those of d-tubocurarine. Perhaps the analogy of a spectrum will make things clearer. If d-tubocurarine and gallamine are placed at the extreme red end, laudexium would occupy a position comparable to that of the orange, while the so-called depolarizing blockers would be placed at the blue and violet end.

I apologize to Dr. Collier for having overlooked his 1953 article.

A. R. HUNTER
Manchester Royal Infirmary

FLOW RATE IN T-PIECE CIRCUITS

Sir,—In your correspondence columns Bullough (1955) refers to his T-piece technique and a flow rate of 8 l./min and says "in the correspondence which followed, the flow rate was criticized as being too high". I have looked back on this "correspondence" in 1952 and, as far as I can see the only criticism was levelled by me. If I am right in this then Dr. Bullough's statement is entirely misleading. I did not criticize the rate recommended from the CO_2 point of view. I criticized its overall cost, and I still maintain we should make for economy wherever it does not conflict with the patients' welfare.

I am in complete sympathy with Dr. Bullough's desire to use nitrous oxide and reduce all pressure in the apparatus. May I suggest that he experiments with the lay-out indicated in the accompanying diagram (fig. 2) as I think it will serve his ideals and prove more economical?

I admit there is nothing new about this except that Ayre's T-piece can be used, the apparatus is unencumbered by valves and there is an open end as suggested in Dr. Bullough's method. I tried it with a manometer after the 1952 article and found that internal pressure seldom varied to 2 cm of water. It seems possible to me that the total flow can be reduced to 3 or 4 l./min, if the nitrous oxide/oxygen ratio is stepped down to 3/1 or 2/1. What the ideal minimum length of the corrugated tube would be I have not worked out, as I doubt whether it matters if the tube is long enough, but as this is so near to Dr. Bullough's technique and as his article inspired it, I wish he would try it as the present nature of my work prevents me giving it a fair trial.

F. F. WADDY
Northampton

REFERENCE
Bullough, J. (1955). *Brit. J. Anaesth.*, **27**, 47.

PROLONGED APNOEA AFTER SUXAMETHONIUM IN MAN

Sir,—The excellent article in the January issue by Argent, Dinnick and Hobbiger, on prolonged apnoea after suxamethonium included a conclusion that I believe might be challenged. I refer to the statement regarding the successful use of neostigmine in some cases of prolonged apnoea.

In a series of seven cases neostigmine was administered to four and considered to be of value in three.

In case IV it would seem understatement to say "neostigmine produced no improvement and it took six hours before normal respiratory rhythm was restored". Fact of the matter is that it strongly suggests that the patient responded in an

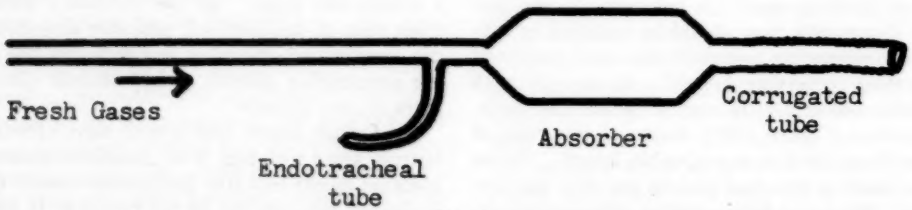

FIG. 2
T-piece arranged with absorber for use with low gas flow rate.

expected manner, with one depolarizing drug enhancing the action of another. On the other hand, the remaining three cases appear to illustrate that this is not always the case and that a coincidental improvement in restored respiration sometimes may be observed. It would be interesting to know the degree of tonicity observed in the other skeletal muscles during the periods of apnoea and subsequent inefficient ventilation.

My associate, Captain Eric Murray, relates the following experience with persistent apnoea following the administration of suxamethonium.

A 50-year-old female, with controlled diabetes, was undergoing an abdominal operation under light, thiopentone induced, cyclopropane anaesthesia with muscular relaxation provided by an intravenous drip of suxamethonium (1 mg suxamethonium in each ml of 5 per cent dextrose in water). Controlled respiration was maintained over a two-hour period. At the end of this time suxamethonium was discontinued, a total of 250 mg having been given, and an unsuccessful attempt to restore respiration was made. Carbon dioxide build-up was tried without effect.

One hour after the suxamethonium had been discontinued, while the patient was still apnoeic, she was due to receive 25 units of insulin and 200 mg of ascorbic acid intravenously. This was given and immediately following its administration she began to breathe and continued to ventilate so effectively that no further assistance was required.

The abdominal muscles were relaxed during the apnoeic period but after breathing was restored additional suxamethonium was required for relaxation during closure of the wound.

Recovery from anaesthesia and relaxation was without further incident.

One wonders if the authors considered the employment of curare to antagonize the action of suxamethonium.

Unless more conclusive clinical and/or experimental evidence is produced any inference that neostigmine will overcome the apnoea caused by a depolarizing drug seems open to criticism.

WILLIAM B. NEFF
98th General Hospital, U.S. Army, Neubrücke/Nahe, Germany.

OUABAIN IN THE TREATMENT OF SHOCK

Sir,—In the third number of volume 27 of this journal, Drs. J. A. G. Horton and M. H. Armstrong Davison have made a strong recommendation for the use of ouabain in the treatment of "shock" when the response to intravenous fluid replacement is disappointing. It is doubtful whether this recommendation is justified by the authors' findings. Their results appear to be based on the effect of ouabain on the mean blood pressure (computed in terms of the diastolic pressure), but they omit to describe the method. If they used the ordinary mercurial manometer they are liable to get unreliable results in determining the "index" of diastolic pressure, as judged by auscultation, since the sounds may sometimes be heard almost to zero cuff pressure in normal subjects.

Changes in the patient's general condition and the systolic blood pressure do not necessarily coincide. The only criterion for the improvement in the patient's condition—apart from odd instances where an irregular pulse became regular—which the authors describe is the effect on the mean blood pressure.

Of 80 administrations of ouabain a rise in pressure occurred in 67. The argument that the rise was due to ouabain is weakened because the majority of instances (57) were complicated by various kinds of fluid replacement. Nothing is stated of how many of the 57 instances warranted the conclusion that the response to transfusion was disappointing. They do not state whether they have measured or made a guess at the blood loss at operation, nor have they defined what they mean by "shock".

This paper makes one think of what would have happened if in every other patient the authors had alternated ouabain with some other pressor drug and lastly, and this is the crux of the whole matter, how does one determine in a patient with hypotension whether the main cause of deterioration lies in the heart, or in the vessels, or both, and how serious is the condition?

R. P. HARBORD
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Sir,—We have read Dr. R. P. Harbord's letter with great interest. Criticism from such a source deserves careful attention, and while we feel that it is right in principle, yet we also feel that here it is hypercritical.

He need not be unduly anxious regarding our use of the mean blood pressure (diastolic blood pressure + ⅓ pulse pressure). The results computed in terms of systolic blood pressure are essentially similar (81 per cent rise; 12 per cent fall; 7 per cent no change). The mean blood pressure was chosen as a convenient comparative index which would take systolic and diastolic values into account.

Omission to describe the method by which the blood pressure was measured was due to a desire to be concise. We do not think that the method used is a matter of importance. Naturally, the same method was used for all readings in any one case, and the "endpoint" was therefore the same. Variations will be detected whatever method is employed, and it is upon these variations that our results are based.

We agree that changes in the patient's general condition and in the systolic blood pressure do not necessarily coincide, but there is often a correlation between blood pressure and physical state, especially when certain vasopressor or depressor drugs have not been given. It is only the blood pressure and pulse rate which are susceptible to easy measurement, and the pulse rate is not greatly influenced by ouabain.

"Nothing was stated of how many of the 57 instances warranted the conclusion that the response to transfusion was disappointing" because it was true in all these cases. Had the response to fluid replacement been satisfactory, no ouabain would have been needed or given. Blood loss was not accurately measured, and this criticism may have some validity. However, we thought that fluid was adequately replaced, and we are sure that there was no gross under-replacement. We plead guilty to not giving a definition of shock, and we doubt if any definition has yet been made which is entirely adequate. To attempt such a definition would surely call down wrath, while use of the term without exact definition implies a state which is at least well-known although difficult to describe.

We attempted, in our list of indications for the use of ouabain, to depict the type of clinical situation which we envisaged. In some instances ouabain was given prophylactically to guard against possible circulatory depression during anaesthesia, sometimes blood loss was severe as in our *Case III*, on other occasions blood loss was normal for the particular operation, yet hypotension had occurred. We would emphasize that these results were obtained in the course of routine practice, fluid replacement being used as indicated. We did not feel justified in withholding it solely to judge the effect of ouabain, hence the number of occasions where it was administered alone were necessarily few.

One can only guess in practice at the underlying cause of a patient's hypotension, but we believe that in ouabain the anaesthetist has a useful drug, free from some of the disadvantages of conventional pressor agents.

We think that the question "how does one determine in a patient with hypotension whether the main cause of deterioration lies in the heart, or in the vessels or both?" is at least partially answered in our paper by the therapeutic test: if the condition responds to ouabain but not to fluid replacement, presumably the failure with fluid is in part due to cardiac insufficiency. How serious the condition is depends on the circumstances, but a measure which hastens the restoration of normal blood pressure, thus shortens the period of hazard to the patient. He is a brave man who can determine limits to the safe degree and duration of hypotension.

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